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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1946

ORIGINAL ARTICLES

THE SPERMATOGENIC ACTIVITY OF Δ^5-PREGNENOLONE AND OF ITS ESTERS*

By G. Masson, Ph.D.

MONTREAL, P. Q., CANADA

(From the Institut de Médecine et de Chirurgie expérimentales, Université de Montreal)

Δ^5-Pregnenolone possesses a considerable degree of spermatogenic activity as shown by its ability to prevent the testicular atrophy normally elicited by hypophysectomy,[1,5,6,7,12] estradiol[2] or small doses of testosterone.[14] Considered until recently a hypothetic intermediary in the biogenesis of the steroid hormones,[13] it proved to be a physiologic body constituent since Ruzicka and Prelog[12] isolated it from pig testes. Unlike the most active spermatogenic steroids, pure Δ^5-pregnenolone does not possess any undesirable action (*e. g.*, Leydig cell atrophy[19]), therefore it is likely to become a useful therapeutic agent. In this paper we report on recent investigations concerning the nature of the spermatogenic activity of Δ^5-pregnenolone and of its acetate, propionate and benzoate. The melting points of the highly purified samples which we used for this work were: free compound 187° to 189° C., acetate 146° to 147° C., propionate 119.5° to 120.5° C. and benzoate 191° to 192° C.

Effects on Hypophysectomized Rats. A first series of experiments was performed on immature albino rats weighing 40 to 60 gm. (average 50 gm.) which were divided into 11 groups of 10 animals each. Treatment commenced on the day of the operation and was continued for a period of 10 days. At autopsy, the testis and the accessory sex organs were removed, fixed in "Susa," weighed and sectioned. The sella turcica was always carefully examined to ascertain the completeness of the operation. Each compound was given at 2 dose levels, namely 1 and 2 mg. a day dissolved in 0.2 cc. of oil. There were also 3 groups of controls: the first and second consisted of normal untreated rats sacrificed respectively on the 1st and 11th day of the experiment; the third consisted of hypophysectomized untreated animals.

As indicated in Table 1, none of these compounds assured normal testis growth in the absence of the hypophysis. At best they maintained this organ approximately at the degree of development which had been attained at the time of hypophysectomy. None of the esters proved more active than the free compound. That the benzoate appeared least active is probably due to its comparatively slow absorption rate. There was no marked difference between the effects at the 1 mg. and the 2 mg. dose levels.

Similar experiments were performed in

* The expenses of this investigation were defrayed through a grant received from the Frank W. Horner Foundation of Montreal.

The steroids were generously supplied by Dr. Elofson of F. W. Horner Limited, Montreal, and the luteinizing hormone (A. P. L.) by Dr. Stanley Cook of Ayerst, McKenna & Harrison Limited, Montreal.

adult albino rats weighing 150 to 180 gm. (average 160 gm.). They were divided into 9 groups (7 experimentals and 2 controls) of 6 animals each. The steroids were either injected at the daily dose level of 2 mg. in 0.2 cc. of oil or implanted in the form of two 10 mg. pellets. The 2 groups of controls consisted respectively of intact and hypophysectomized animals. The results summarized in Table 2 essentially confirm our conclusion that testis weight is merely maintained at about the normal level. Perhaps the acetate is slightly more active. Pellet implantation did not maintain the testis as effectively as injections. Histologic examination showed active spermatogenesis in all these hypophysectomized adult treated rats.

To complete our study on the spermatogenic effect of Δ^5-pregnenolone, the following experiment was performed in order to determine whether this compound—alone or in combination with gonadotrophic hormones—is able to restore an already atrophic testis to its normal condition. This combined treatment was tried because it is known that a peripheral synergism exists between the gonadotrophic hormones and the folliculoids in the hypophysectomized female.[11,17]

TABLE 1.—EFFECT OF Δ^5-PREGNENOLONE ON IMMUNE HYPOPHYSECTOMIZED RATS

Name of compound	Daily dose (mg.)	Wt. of testis (mg.)
Controls non-operated	..	306 (71)*
Controls non-operated, killed after 10 days	..	378 (20)
Controls hypophysectomized	..	91 (6)
Δ^5-Pregnenolone	1	226 (49)
	2	296 (35)
Δ^5-Pregnenolone acetate	1	179 (15)
	2	195 (37)
Δ^5-Pregnenolone propionate	1	214 (52)
	2	188 (28)
Δ^5-Pregnenolone benzoate	1	166 (31)
	2	121 (6)

* Standard error. The standard errors indicated are calculated by the formula:

$$S.E. = \pm\sqrt{\Sigma d^2 f/n(n-1)}.$$

TABLE 2.—EFFECT OF Δ^5-PREGNENOLONE ON ADULT HYPOPHYSECTOMIZED RATS

Name of compound	Daily dose (mg.)	Wt. of testis (mg.)
Controls non-operated	..	2162 (61)*
Controls	..	7–8 (46)
Δ^5-Pregnenolone	2	1600 (14)
Δ^5-Pregnenolone acetate	2	2051 (120)
Δ^5-Pregnenolone propionate	2	1747 (49)
Δ^5-Pregnenolone benzoate	2	1430 (99)
Δ^5-Pregnenolone	Pellets	1492 (105)
Δ^5-Pregnenolone acetate	Pellets	1698 (59)
Δ^5-Pregnenolone propionate	Pellets	1706 (63)

* Standard error.

Adult rats weighing 80 to 100 gm. were hypophysectomized. They were not treated for a period of 14 days so as to permit a severe testis involution. On the 15th day, the animals were divided into 4 groups of 6 animals each and treated for 14 succeeding days as follows: Group I untreated, Group II Δ^5-pregnenolone (2 mg. a day), Group III Δ^5-pregnenolone (2 mg. a day) plus luteinizing hormone (100 I.U. a day), and Group IV luteinizing hormone

(100 I.U. a day). On the 15th day of treatment, that is, on the 29th day after hypophysectomy, the animals were sacrificed. The results are expressed in Table 3. From these data it appears that Δ^5-pregnenolone alone or in combination with the luteinizing hormone is completely ineffective in increasing the testis weight after hypophysectomy. The testis weight is approximately the same in Groups I and II on one side and in Groups III and IV on the other. On histologic examination the germinal epithelium was markedly atrophic in all groups. The Leydig cells were atrophic in Groups I and II while in Groups III and IV they formed large clumps which account for the increase in testis weight over the controls. This interstitial cell stimulation manifests itself furthermore by the marked development of the seminal vesicles and prostate.

Table 3.—Effects of Δ^5-Pregnenolone and Luteinizing Hormone on Hypophysectomized Rats

Group	Treatment	Daily dose	Testis (mg.)	Seminal vesicles (mg.)	Prostate (mg.)
I	....	..	196 (33)*	9 (5)*	14.5 (7)*
II	Δ^5-Pregnenolone	2 mg.	189 (10)	10.5 (4)	17.5 (7)
III	Δ^5-Pregnenolone + L. H.	2 mg. 100 I.U.	326 (21)	134 (16)	101 (8)
IV	L.H.	100 I.U.	408 (30)	133 (13)	118 (10)

* Standard error.

Effects on Estradiol Treated Rats. The first experiment is merely a repetition of a previous work made by Albert and Selye.[2] It was undertaken because at that time a sample of the pregnenolone used by these authors showed a fairly strong folliculoid activity at the daily dose of 3 mg.,[16] while with the present sample, a dose of 50 mg. was necessary to obtain the same result. It is therefore considered possible that impurities might have masked some of the spermatogenic effect of this compound.

Male albino rats weighing 150 to 180 gm. (average 160 gm.) were divided into 4 experimental and 1 control groups of 6 animals each. The treatment was as follows: Group I consisted of untreated controls, Group II estradiol (2 mg. a day), Group III estradiol (200 γ a day), Group IV estradiol (2 mg. a day) plus pregnenolone (10 mg. a day), and Group V estradiol (200 γ a day) plus pregnenolone (10 mg. a day). Both steroids were in oil solution. On the 15th day of treatment the animals were killed and the organs taken for weight. The results expressed in Table 4 evidently show that the degree of protection given by Δ^5-pregnenolone varies with the amount of damage caused by the 2 doses of estradiol. This protecting effect applies to the spermatogenic epithelium as indicated by testis weight as well as to the Leydig cells as indicated by the weight of the seminal vesicles. It has been shown by Selye and Albert[15] that Δ^5-pregnenolone has no effect on the seminal vesicles of the castrated rat. Incidentally the adrenal stimulation caused by estradiol is also slightly diminished by pregnenolone.

In order to study the effect of Δ^5-pregnenolone on the regeneration of the testis, experiments were performed on rats previously treated with estradiol. Albino rats weighing 150 to 180 gm. (average 160 gm.) were divided into 6 groups of 10 animals each: 5 experimentals and 1 control. Group I received estradiol for 21 days then remained untreated for 21 days; Group II received estradiol for 21 days then Δ^5-pregnenolone for another period of 21 days; Group III remained untreated for 21 days then received estradiol plus Δ^5-pregnenolone for another period of 21 days; Group IV received Δ^5-pregnenolone for 42 days; Group V remained untreated for 21 days then received

estradiol for another period of 21 days; Group IV consisted of untreated controls.

Estradiol was administered in the form of 2 pellets of 10 mg. each per animal which were removed whenever the treatment was discontinued; Δ^5-pregnenolone was injected at the daily dose of 10 mg. (oil solution at the concentration of 25 mg. per cc.). On the 43rd day of treatment the animals were sacrificed and the tissues were removed for weight and histologic examination.

between Groups IV, V and VI, it is doubtful that the difference is very significant between Groups I, II and III.

In order to evaluate these results it was necessary to repeat a similar experiment using comparatively Δ^5-pregnenolone and testosterone. For this purpose 5 groups of 10 albino rats weighing 40 to 65 gm. were used. After an initial period of treatment consisting in the implantation of two 10 mg. pellets of estradiol per animal for a period of 14 days,

TABLE 4.—EFFECTS OF Δ^5-PREGNENOLONE IN RATS TREATED WITH VARIOUS DOSES OF ESTRADIOL

Group	Treatment with daily dose	Testis (mg.)	Seminal vesicles (mg.)	Adrenals (mg.)
I	....	2455 (97)*	282 (34)*	25 (1.5)*
II	Estradiol, 2 mg.	1124 (103)	77 (11)	48 (5)
III	Estradiol, 200 γ	1416 (126)	87 (9)	42 (3.4)
IV	Estradiol, 2 mg. + Pregnenolone, 10 mg.	1864 (175)	115 (4.8)	43 (2.7)
V	Estradiol, 200 γ + Pregnenolone, 10 mg.	2018 (155)	161 (2.5)	36 (2.9)

* Standard error.

TABLE 5.—EFFECT OF Δ^5-PREGNENOLONE IN ESTRADIOL TREATED RATS

Groups	Pretreatment	Treatment	Testis (mg.)	Seminal vesicles (mg.)	Adrenals (mg.)	Spermatogenesis from 0 to 4
I	Estradiol	....	911 (85)*	60 (7.8)*	49 (1.5)*	1.30
II	Estradiol	Pregnenolone	826 (76)	66 (6.6)	45 (2)	1.10
III	..	Estradiol + Pregnenolone	742 (85)	51 (2.5)	44 (2.7)	0.85
IV	Pregnenolone	Pregnenolone	2028 (73)	370 (25)	32 (1.5)	4.00
V	..	Estradiol	519 (31)	47 (1.4)	39 (2.8)	0
VI	..	..	2098 (69)	375 (31)	27 (0.7)	4.00

* Standard error.

From Table 5 it appears that at the dose of 10 mg. Δ^5-pregnenolone (1) has no damaging effect on the testis (compare Groups IV and VI), (2) prevents to a certain degree the testis atrophy produced by estradiol (compare Groups III and V), (3) does not significantly influence the regeneration of testis previously damaged by estradiol under these conditions (compare Groups I and II).

The testes were histologically examined and the degree of spermatogenesis expressed on a scale of 0 to 4. In the table we give the average with, in brackets, the range in the degree of spermatogenesis. While the differences are very striking

the various groups were subsequently treated in the following manner: Group I remained untreated; Group II received pregnenolone (10 mg. a day); Group III received testosterone (10 mg. a day); Group IV received testosterone (2 mg. a day); Group V received pregnenolone (10 mg. a day) plus testosterone (2 mg. a day). On the 29th day after pellet implantation the animals were killed. The results are summarized in Table 6. It is obvious that a marked difference exists between the activity of Δ^5-pregnenolone and that of testosterone. Testosterone at the 2 mg. dose level does not influence to any great extent the regenera-

tion of the testis, while at the 10 mg. dose level it accelerates it markedly. On the contrary pregnenolone at the dose of 10 mg. maintains the testis in atrophic state by inhibiting the regeneration process. However, it is interesting to note that the seminal vesicles are perhaps more stimulated in Group II which received pregnenolone than in Group I which remained untreated. This would suggest that pregnenolone which is not testoid has stimulated the secretion of endogenous testoid hormone.

TABLE 6.—EFFECT OF Δ^5-PREGNENOLONE AND TESTOSTERONE ON RATS PREVIOUSLY TREATED WITH ESTRADIOL

Group	Treatment with daily dose	Testis (mg.)	Seminal vesicles (mg.)
I	....	527 (65)*	49 (4)*
II	Δ^5-Pregnenolone, 10 mg.	237 (15)	61 (6)
III	Testosterone, 10 mg.	888 (71)	822 (51)
IV	Testosterone, 2 mg.	410 (71)	246 (10)
V	Δ^5-Pregnenolone, 10 mg. + Testosterone, 2 mg.	344 (21)	204 (10)

* Standard error.

Due to the significance of these results from the point of view of the mode of action of the spermatogenic steroids, it seemed to the author that before discussing such a possibility, another experiment should be undertaken. Rats weighing 85 to 95 gm. were used and divided into 4 groups pretreated for the same length of time with estradiol. The treatment was as follows: Group I untreated controls, Group II pregnenolone (10 mg. a day), Group III testosterone (5 mg. a day) plus pregnenolone (10 mg. a day) and Group IV testosterone (5 mg. a day). The animals were killed after 10 days of treatment. The average testis weight was respectively 810, 261, 583 and 547 mg. for each of the successive groups. These data, therefore, confirm the previous conclusions concerning a difference in the way of action between testosterone and pregnenolone.

Summary and Conclusions.. By spermatogenic activity of steroid compounds, we understand their ability to prevent testicular atrophy following hypophysectomy, treatment with estradiol, small doses of testosterone or non-specific agents. The observations of Nelson,[8,9,10] Cutuly,[3,4] Selye and Friedman[18] and Masson[7] showed that these steroids can be divided into 2 groups: those which are capable of restoring spermatogenesis in a testis previously rendered atrophic by hypophysectomy (compounds of the testosterone and androstenediol type), and those which do not possess this property (compounds of the progesterone type). The experiments reported in this communication support the value of this classification. We have shown that testosterone accelerates, while Δ^5-pregnenolone inhibits the regeneration of the atrophic testis. One can say that testosterone is an *active* spermatogenic compound which directly stimulates the proliferation of the germinal epithelium, while Δ^5-pregnenolone is a *passive* spermatogenic agent, whose action consists merely in protecting and maintaining the testis in the condition in which it is at the commencement of treatment.

This classification may serve as a basis for the rational selection of gonadotrophic steroids for clinical use. The steroids which belong to the testosterone and androstenediol type should only be used when the testis is already damaged because in the case of almost normal testes, there is a danger of causing Leydig cell atrophy by such treatment and this may represent a greater evil than the diminution in the spermatogenesis. Conversely Δ^5-pregnenolone should only be used if a comparatively normal testis is to be pro-

tected against subsequent damage. With this compound there is no reason to fear any unpleasant side-effects since at the daily dose of 10 mg. it is practically devoid of folliculoid, testoid and corticoid activities and possesses only weak luteoid properties.[6] These conclusions are in accord with those of Selye and Albert[14] who suggested that "by combining moderate doses of testosterone with a non-testoid compound such as pregnenolone, therapeutic doses of testosterone may be given in cases of eunuchoidism without the danger of producing testis atrophy."

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TESTOSTERONE IN ANGINA PECTORIS

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The problem of treatment of angina pectoris continues to vex the internist, and while nitroglycerin remains our most effective agent in relieving each attack as it occurs, the search for a medication which will eliminate or greatly reduce the frequency of attacks in those affected by the disease continues.

Testosterone preparations have been recommended, and recently the use of testosterone propionate injections was brought to popular attention by an article in the lay press and a book by a popular writer. Interest in the value of this drug, which is rather expensive and requires a somewhat tedious course of injections, continues high.

Review of the literature reveals that in 1940 Walker[15] first reported definite subjective improvement, increased emotional and exercise tolerance, decreased severity of pain and general increase in strength in 4 of 5 patients suffering from angina pectoris. In a later report the same author obtained improvement in 7 of 9 men and 2 of 3 women, but 1 of the men had a coronary occlusion during the course of treatment.

Lesser,[5,6] in 2 enthusiastic articles, claimed excellent results in a total of 41 men and 5 women, treated with testosterone propionate, 25 mg. intramuscularly every 2 to 5 days for 5 to 25 doses, with an average of 11 doses. Improvement appeared in 4 to 6 weeks and was well sustained. Hamm[2] also reported favorably.

Sigler and Tulgan,[11] treating 20 cases which had been demonstrably relieved by nitroglycerin, noted marked relief in 11 and no relief in 4. Strong and Wallace,[13] in 1944, reporting 20 cases, obtained marked relief in 6 and slight to moderate, transient improvement in 11, with no relief in 3, and concluded that hormones have some value in treatment of angina pectoris.

Goldman and Markham[1] treated 7 cases of effort syndrome which they considered a complication of the male climacterium, and noted favorable response in 6. The seventh which they diagnosed as true cardiac angina, did not respond. McGavack[9] treated 8 similar cases not responding to nitrites and observed prompt and dramatic relief from 24 to 48 hours. He suggested that this response be used as a diagnostic test to differentiate functional "climacteric" angina from true "organic" angina. He stated further that the pains of organic heart disease have never responded rapidly and completely, if at all, to testosterone. He felt that the testosterone orally was as effective as testosterone parenterally administered.

Levine and Likoff,[7] in 1943, analyzed 19 cases of definite angina pectoris, 3 of whom had coronary occlusion, treated with 25 mg. of testosterone propionate intramuscularly 3 times a week for 4 to 7 weeks. Marked temporary improvement was noted in 5 cases but there was no change in 11 cases. These authors were unable to conclude that testosterone was of any benefit, considering the vagaries of the disease. Hurxthal[4] reported equivocal results with oral and intramuscular administration in 19 cases, and disappointing results from pellet implantation. Riseman[10] classified testosterone among agents of no value in treatment of angina pectoris.

Waldman,[14] in November 1945, endorsed testosterone as a treatment for true angina pectoris on the basis of his experience in 10 cases, and what he presents as objective electrocardiographic evidence of

increased exercise tolerance. This evidence is not convincing.

The conflicting reports suggested to us that testosterone preparations had value in some condition which, if not true angina, was similar enough in its clinical manifestations to lead to considerable confusion.

Obviously, not all recurrent chest pain is angina and not all precordial pain is angina. The pain of angina is characteristically retrosternal and not precordial. A syndrome has been described due purportedly to failure of gonadal function in the male, occurring usually after the age of 30, but as early as 25 years of age, and termed the male climacteric. Symptoms of this condition include fatigability, palpitation, weakness, dyspnea, abdominal pain and nervousness. We have noted that a feeling of tightness in the chest and of precordial or rarely substernal aching or fullness might also be present, suggesting angina pectoris. This has been previously described.[9] Considerable concern over the possibility of heart disease was often apparent, and in many instances the true retrosternal pressure pain, choking and vasomotor phenomena of angina pectoris were present in addition to and apart from the less specific symptoms of male climacteric. The complaints of impotence of rather recent development, in conjunction with hot flashes and the other symptoms attributed to the male climacteric were accepted as identifying a particular syndrome, whether or not symptoms of true angina pectoris, were also present. Thus, 2 clinical entities, true angina pectoris, and a somewhat different chest discomfort related to the male climacteric came immediately under observation; both syndromes were coëxistent in several patients. The question of whether the symptoms attributed to the male climacteric were altogether due to it, or due in part to anxiety neurosis or so-called neurocirculatory asthenia did not seem to require consideration in the present connection.

We set out to answer the following questions:

1. Does testosterone propionate by injection or methyl testosterone by sublingual administration have any value in treatment of true clinically diagnosable angina pectoris?

2. Do either of these preparations have a field of usefulness in relieving the chest discomfort associated with male climacteric or nervous instability occasionally encountered in individuals of the age group commonly subject to angina?

3. Is there any difference in the effect of the drug depending on the route of administration, whether parenteral or sublingual?

Materials and Methods. Twenty-four male patients, age 33 to 76 years (average 54 years), all but 1 of whom had been referred to us with the provisional diagnosis of angina pectoris, were studied. They had had symptoms from 2 to 72 months before treatment was begun, with an average duration of illness of 16 months prior to treatment. Electrocardiograms were obtained in all cases and Roentgen ray study of the chest performed when indicated.

On the basis of the clinical and electrocardiographic findings, patients were classified by diagnoses into 3 main groups as follows:

Group 1. True angina pectoris—21 patients.

Group 2. Male climacteric with chest discomfort but not true angina pectoris—2 patients.

Group 3. Male climacteric symptoms alone—1 patient.

Three subgroups appeared. These were:

Subgroup 1. Symptoms of male climacteric in addition to true angina pectoris—10 patients.

Subgroup 2. Cardiac neurosis with true angina pectoris—2 patients.

Subgroup 3. Cardiac neurosis with climacteric syndrome—1 patient.

Valvular heart disease was present in 2 cases of the series, due in both cases to rheumatic heart disease. In 1 aortic stenosis and insufficiency and mitral stenosis

were present and in the other minimal aortic stenosis alone.

Hypertension, with blood pressure consistently greater than 140/90 was present in 6 cases.

Four patients had had definite coronary occlusion proved by history and electrocardiographic changes before the treatment was instituted, and 4 other patients may have had old myocardial infarction, although their histories were not conclusive and their electrocardiograms were only suggestive.

TABLE 1.—RESULTS IN RELATION TO DIAGNOSTIC CATEGORY

No. patients	Diagnostic category	Results: No improvement	Slight improvement	Moderate improvement	Marked improvement	Death	Total courses
21	True angina pectoris	11	4	4	2*†	1	22
2	Climacteric with chest discomfort (not angina pectoris):						
	Climacteric (general)	..	..	..	2‡§		2
	Chest discomfort	..	..	..	2‡§		
1	Climacteric	..	..	..	1	..	1
10	Climacteric symptoms with true angina pectoris:						
	Climacteric	2¶			6	1	10
	Angina	5	2	1	1	1	
2	Cardiac neurosis with true angina pectoris	1	..	..	1†	..	2
1	Cardiac neurosis and climacteric	..	..	..	1§	..	1

* 1 patient was 75% improved.
† 1 patient had a large psychic element. Said he "felt like a new man" after the third injection.
‡ All symptoms helped by 1 injection (1 case).
§ Relief after 4 weeks' treatment, Schedule C (alcoholic with severe cardiac neurosis).
¶ No record kept as to effect of treatment on climacteric symptoms in 1 additional case.

Two routes of administration were used, intramuscular and sublingual. Twenty-five courses were given, 1 patient receiving both sublingual and intramuscular medication. The dosage schedules are indicated in Table 2.

Results with reference to the anginal symptoms were evaluated and classified as: No Response, Slight, Moderate, or Marked Improvement. There was 1 death after treatment was begun. Evaluation was based on: (1) Questioning the patient as to his subjective response. (2) Questioning the patient as to the amount of nitroglycerin required. (3) The response to the exercise tolerance test of Master.[12] This test was applied in only 7 cases and no change was apparent as a result of treatment in any. The test was not used more extensively because of the difficulty of maintaining the same conditions as to room temperature, physical status of the patient and time of day, all of which may influence the result and make it difficult to interpret.

Results with reference to the symptoms of male climacteric or of cardiac neurosis were classified simply as: Relieved or Not Relieved, on the basis of the patient's replies to questioning.

Results. The results we obtained are summarized in the following tables:

Table 1 shows the results of treatment according to diagnostic category.

Of the 21 patients with true angina pectoris who received a total of 22 courses of treatment, 11 showed no improvement, 4 showed slight, 4 moderate, and 2 marked benefit. One died of coronary occlusion 72 hours after treatment was begun. The occlusion occurred after 3 doses of methyl

testosterone had been taken (see Table 2). Of the 2 patients with marked improvement, 1 was considered about 75% relieved, but was not cured, and 1, who showed a large psychogenic factor and was classified also in the group of cardiac neurosis with true angina said he "felt like a new man" after the third injection. These results are not startling and hardly justify any claim that these drugs in the dosage employed are of real benefit in true angina pectoris.

5 cases, slightly improved in 2, moderately improved in 1, and markedly improved in 1. One patient, previously mentioned, died shortly after treatment was instituted. Again the lack of parallelism between the responses of the 2 groups of symptoms is demonstrated, and the lack of value of testosterone in treatment of angina is evident.

Two patients with significant cardiac neurosis and true angina pectoris were treated. One was not helped and the

TABLE 2.—RESULTS IN RELATION TO DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION

		Angina pectoris (21 patients)					Climacteric (13 patients)		
Schedule	Total No. courses	No response	Slight improvement	Moderate improvement	Marked improvement	Died	Relieved	Not relieved	Died
A	1	1							
B	3	1	1	1	..	..	2		
C	7	1	1	2	1	..	3		
D	5	2	1	1	1	..	1*		
E	8	6	1	..	..	..	1	4	
E'	1	Patient had coronary occlusion 24 hours after treatment started and died 48 hours later				1	..	..	1

* Effect on symptoms of climacteric not recorded in 1 additional case.

Schedule	Total weekly dosage (mg.)
A. 25 mg. testosterone propionate intramuscularly once weekly for 6 weeks	25
B. 25 mg. testosterone propionate intramuscularly twice weekly for 6 weeks	50
C. 25 mg. testosterone propionate intramuscularly 3 times weekly for 4 weeks	75
D. 5 mg. methyl testosterone sublingually twice daily for 6 weeks	70
E. 5 mg. methyl testosterone sublingually 3 times daily for 4 weeks	105

The 2 patients with climacteric symptoms associated with chest discomfort consisting of precordial pain or oppression, dyspnea and left mammary pain were both markedly benefited with regard to both general symptoms and chest discomfort. Although the number is small, the drug seems to have considerable value here.

One patient with climacteric symptoms alone was greatly helped.

In the group of patients with angina were 10 whose angina was complicated by symptoms of male climacteric. The climacteric symptoms were unrelieved in 2 of these. There was no record kept of results in 1, and relief was obtained in 6. The symptoms of angina did not react in a similar fashion, but were unrelieved in other patient, previously mentioned, in whom the psychogenic factor was hard to evaluate accurately but in whom it was felt true angina was present, was relieved.

One patient with severe cardiac neurosis and precordial discomfort associated with the climacterium was relieved.

Table 2 shows the influence of the route of administration and dosage on the effectiveness of the drug.

With regard to the symptoms of angina pectoris, it apparently made little difference whether the drug was given sublingually or parenterally as little benefit was obtained anyway.

The climacteric symptoms were more uniformly relieved by parenteral administration of testosterone propionate than by

sublingual administration of methyl testosterone in the dosage employed.

A note regarding dosage of the drug for sublingual use is in place here. The weekly total dose is shown in the table. The effective dose of testosterone given orally is supposed to be 3 or 4 times the intramuscular dose.[12,16] The effective intramuscular dose in our experience was 50 to 75 mg. per week. The expected effective oral dose would therefore be 150 to 300 mg. per week. The dosage of methyl testosterone linquets for sublingual administration is supposed to be from one-half to two-thirds of the calculated oral dosage.[8,12] Thus an effective dose might be expected to fall between 75 and 200 mg. each week. Our patients received either 70 or 105 mg. each week. These dosage schedules were chosen for the sake of convenience, and because it appeared from studying other reports that they should provide sufficient medication. In this connection it is noteworthy that Heller and Myers,[3] in treating the male climacteric, found sublingual methyl testosterone unsuitable because it was ineffective or produced undesirable side reactions, such as burning of the mouth, swelling of the gums, nausea, vomiting, heartburn, weakness of the legs, tinnitus, vertigo and headache. In 2 of our cases, untoward symptoms were associated with sublingual administration, 1 patient claiming that methyl testosterone kept him awake and the other that it caused indigestion. Both felt that the attacks of angina increased in frequency while taking the drug.

Conclusions. Although this study deals with a small and statistically insufficient group of cases, the indications seem fairly clear.

The questions posed earlier may now be answered.

1. Neither testosterone propionate intramuscularly nor methyl testosterone sublingually appears to have any value in the treatment of angina pectoris.

2. Testosterone preparations appear to be of definite value in relieving the chest discomfort sometimes associated with the male climacterium or the similar precordial ache of neurocirculatory asthenia occasionally encountered in individuals in the age group commonly subject to angina pectoris.

3. In their field of usefulness, parenteral administration of 25 mg. of testosterone propionate 2, or preferably 3, times weekly is to be preferred to the rather ineffective administration of methyl testosterone sublingually in doses of 10 or 15 mg. daily.

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ECHINOCOCCOSIS IN ICELAND

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Hydatid cysts have during the last centuries been of frequent occurrence in Iceland. Reliable statistics are not available, but Schleisner[10] estimated that 1 out of 7 persons suffered from this disease about the middle of the 19th century. Of 2600 patients of all ages which Icelandic physicians had examined at that period, according to official medical reports 1 out of every 8 had liver disease. But of Schleisner's 326 patients, 1 out of every 6 had hydatid cysts. However, Magnússon[9] found many faults with Schleisner's calculations, regarding these estimates as far too high.

Schleisner's estimates have been cited in the medical literature, and up to the present they have been the basis of information upon which the medical world has depended with regard to this disease in Iceland.

A little later Finsen[6] found 298 patients with hydatid cysts out of a total number of 7044, or 1 of every 22.6. This author thought this number proportionally too high, as many patients with this disease came to him from outside his district. By counting hydatid patients in families of his personal acquaintance he found 13 patients in 46 families with a total of 561 members, or 1 in 43. Finsen inclined to conclude that 1 of every 40 to 50 inhabitants in this country harbored hydatid cysts.

In a monograph on hydatid disease Jonassen[7] criticized Finsen's calculations, chiefly on the ground that Finsen had not seen the majority of his patients and had only operated on 50 of 298. Jonassen tried to form an estimate by inquiring among 13 medical officials whom he regarded as trustworthy and obtaining reports from them on all known patients with hydatid cysts in their districts, where the total number of inhabitants was known.

The result of this inquiry was that out of 9982 individuals 122 were found with clinically manifest hydatid cysts or 1:82. Jonassen considered this a low estimate, because Reykjavik was included, where he found only 1 patient among the 2000 inhabitants. By omitting Reykjavik the ratio was brought up to 1:61, which he considered a reasonable estimate for the whole country.

The only available autopsy reports previous to the one here presented are from the leprosy hospital outside Reykjavik where Bjarnhédinsson[1] found hydatid cysts in 26 out of 86 autopsies, or in 30%. G. Magnússon, however, thought these findings not representative for the whole population, as the lepers were from homes which might be expected to have a higher rate of echinococcosis than the average. Magnússon[9] tried to make an estimate of the infestation rate of the entire country, taking Jonassen's calculations as a basis for his own, which were made 30 years later (1914). By comparing the number of his patients with hydatid cysts with those of Jonassen's time, he found the morbidity rate only one-fourth of what it had been in 1882. Magnússon's monography (written in 1913) concluded: "There should be not more than 300 patients in the whole country, and their number is steadily decreasing, as the dead patients outnumber the fresh crops."

Hydatid Cysts Found at Autopsies. 1930–1944 (incl.). In this 15 year period, 1231 autopsies were performed. In this number, stillborn children and those under 14 days old have been omitted. On the other hand, 2 cases are included in whom no parasites were found at the autopsy,

but who had been operated on and the parasites removed.

Table 1 shows the number of autopsies performed each year and the number of individuals harboring hydatid cysts. According to this survey, a total of 60 individuals were infested with echinococcus granulosus or showed unmistakable signs of having been infested. This corresponds to 1 echinococcus carrier out of every 20.5.

TABLE 1.—NUMBER OF AUTOPSIES AGAINST ECHINOCOCCUS CASES, 1932–1944

1932	32:5	15.6%
1933	74:4	5.4%
1934	71:4	5.6%
1935	96:3	3.1%
1936	91:1	1.1%
1937	118:6	5.1%
1938	115:2	1.6%
1939	88:7	8.0%
1940	98:4	4.0%
1941	115:6	5.2%
1942	121:7	5.8%
1943	84:3	3.6%
1944	125:8	6.4%

TABLE 2.—ECHINOCOCCOSIS FOUND IN VARIOUS AGE GROUPS (34 MALES, 26 FEMALES)

Age	Total autopsies	Echinococcus cases	%
0–20	239	0	0
21–30	193	1	0.5
31–40	199	1	0.5
41–50	170	4	2.4
51–60	179	13	7.3
61–70	153	21	13.7
71–90	98	20	20.0
	1231	60	4.9

Table 2 shows that hydatid cysts are chiefly found in the higher age groups, but are comparatively rare among the young, no cyst being found in anyone under 20 years of age. In those over 70 years of age hydatid cysts were found in 20 (20%), but in all persons past 60, numbering 151, hydatid cysts were found in 41 (16%). In those past 60 years of age 1 of every 6 harbored 1 or more echinococcus cysts.

These are the people who in Magnússon's time were in their prime of life. As there is no reason to assume that echinococcus carriers have been spared in preference to other people, the conclusion is justified that in 1913 every 6th person above 30 years of age has been infested with echinococcus.

All the authors mentioned above, who have estimated the distribution of echinococcosis, have based their figures on the number of echinococcus patients, *i. e.*, individuals who have had inconveniences from their hydatid cysts, sufficient to classify them as patients. Obviously no clear-cut line can be drawn between healthy and sick persons in this respect. This method of previous authors was only dictated by necessity, when no other way was possible to discover the actual percentage of infestation and all authors realized the lack of exactness in their estimates, pointing out that reliable information will not be obtained until autopsy reports are available.

Localization. By far the most of the parasites were localized in the liver (56 out of the total of 60). In 4 cases hydatid cysts were found in the peritoneum; in a 59 year old female 2 cherry-sized calcified parasites were found in the omentum. A 62 year old male had a parasite of hen's egg size adherent between the ileum and the cecum, and in a 75 year old male a parasite of similar size was found on the right side of the urinary bladder in the pelvis. In the 4th case numerous secondary cysts up to walnut size were scattered all over the peritoneum. In all these cases one or more cysts were found in the liver.

Other locations were very rare: 2 in the spleen and 2 in the heart, but no hydatid cysts were found in other organs.

Our experience corroborates Claessen's[2] findings, that primary echinococcus cysts in the lungs do not belong to the picture of echinococcosis in this country. We found no hydatid cyst in the lungs in our material.

This distribution is a little different from Jonassen's who found 18% of his material in the kidneys. Of 50 hydatid cysts, 9 were in the kidneys, 3 in the spleen and 1 in the heart. The distribution has therefore been similar with exception of the kidney cysts.

We have a strong suspicion that at least some of Jonassen's kidney cysts were not echinococcus cysts, but only urinary retention cysts which are fairly frequent and may reach considerable size, sufficient to mislead unexperienced investigators. Jonassen evidently has realized that his kidney cases were not reliable, for by sifting his material critically he finally counted only 2 of the 9 as beyond doubt. Certainly 1 of these must have been an echinococcus, because daughter cysts were found in it.

It is worth notice that 2 of the cysts in our material were found in the heart. Probably this localization is not so rare as commonly supposed; it seems more than co-incidental that we found 2 such in a total of 60. One of them was a bladder of cherry size, loosely adherent to the endocardium of the right ventricle. This cyst was found in a 26 year old male from the country who died of phthisis. The parasite was alive and evidently very young, probably not over 2 to 3 years old (the patient had been in a tuberculosis hospital during the previous 2 years, where he could not have an opportunity of infesting himself). The other case was located in the septum ventriculorum and had ruptured into the pericardium. This case has been described elsewhere by us.[5]

Liver Cysts. Of the 56 liver cysts the localization is not mentioned in 8 cases. In the 48 cases in which the localizations are recorded, the parasites were distributed as follows: right lobe, 32 (67%); left lobe, 6 (12.5%); both lobes, 6 (12.5%); ligamentum falciforme or intermediary zone, 4 (8%).

Other investigators (Dew[4]) have found parasites in both lobes only in 2 to 4% of their cases. Our findings correspond with the heavier infestation in this country. All investigators seem to find the parasites 5 times more frequently in the right than in the left lobe.

Cases of Special Interest. CASE 1. No. 67–42. A 47 year old male was brought from the country with the diagnosis subphrenic abscess, but his condition was so bad that operation was not considered advisable, and he died a few days later.

In the pleural sac there were 2500 cc. of purulent fluid. The right lung was completely collapsed, lying as a thin sheet close to the mediastinum and the diaphragm. The lung was adherent to the diaphragm, but close to its border was a perforation through which purulent material passed from below the diaphragm. When the lung was torn from the diaphragm a round opening, 8 cm. in diameter, was discovered in the diaphragm, leading directly into a hydatid cyst of cocoanut size. The adventitia is slightly calcified. The contents are a gelatinous mass with a few collapsed daughter cysts. The cyst is adjacent to the vertebral column and touches the superior surface of the right kidney. No other hydatid cysts were present.

CASE 2. No. 11–1944. In a 59 year old male, who had been operated on for echinococcus 13 years before, symptoms of prostatic hypertrophy and uremia led to death in 3 months.

At *autopsy*, the liver weighed 1750 gm. When the abdomen was opened, an abscess of fist size was opened close to the sternum, below the right curvature. Rests of chitinous membranes pointed to the hydatid origin of the suppuration. The right lobe was malformed by hydatid cysts. One prominent cyst had grown tower-like upwards from the liver on the right side and into the lung, compressing the diaphragm before it, in such a way that it could not be distinguished from the adventitia of the capsule. This cyst was very slightly calcified and contained numerous daughter cysts and foul purulent fluid. The same condition was found in a hydatid cyst close by. The volume of each of these cysts corresponded to that of an apple, the elongated one being a little larger and of oblong shape.

In this case the capsule still protected the surrounding lung tissue, but the cyst was evidently on its way to suppuration into the lung.

CASE 3. No. 63–44. A 51 year old female who had for 14 years been in a lunatic asylum, developed a distention of the abdomen which was thought to be caused by an ovarian cyst. Three days before death she vomited blackish, turbid fluid and had severe pains in the abdomen. Prostration

and collapse followed quickly and led to death.

When the abdomen was opened a huge echinococcus cyst was discovered, which was attached to the right lobe of the liver. The intestines were in several places adherent to the cyst, particularly the transverse colon, the anterior surface of the stomach, duodenum and the descending colon. The diameter of this cyst was 50 cm. and it contained 16 liters of thick, brownish fluid, with clear uncollapsed daughter cysts. From the left inferior surface of the liver another cyst of hen's egg size was suspended. Above the right kidney were 3 hydatid cysts, all together the size of an apple.

This cyst is probably the largest on record, the biggest reported by Devé[3] containing 10.5 liters.

Number and Condition of the Cysts. The size of the cysts varied from pea size to the enormous dimension in the case just described. The old, dead cysts were of varying sizes, most frequently from billiard ball size to that of a large orange. Completely calcified cysts were frequently the size of a billiard ball, and so hard that they could not be cut through with a knife. When sawed through they were frequently found calcified through and through and hardly any rests visible of a parasitic membrane. In most cases only a solitary cyst was found; in some cases they were multiple. The number of cysts in the liver is an indication of the massiveness of the original infestation.

In the liver we found: 1 cyst in 37 cases, 2 cysts in 12 cases, 3 cysts in 5 cases, and 4 or more in 2 cases.

Of 56 hepatic cysts 19 (34%) were multiple. Dew[4] found 31% at operations.

Where multiple cysts were found their condition was usually similar, although the size might vary considerably. Yet one might be found completely calcified and the other only with a chitinous membrane and containing a gelatinous brownish mass. In no case did we find an accompanying cirrhosis, as described by Devé and others.

Comment. These findings must be taken as representative for conditions as they have been during the last 13 years in this country. They are from hospitals in Reykjavik, which receive patients from all over the country, although the majority are inhabitants of Reykjavik. But as a considerable proportion of Reykjavik's inhabitants consists of persons who have been brought up in the country, our material should reflect the present conditions as accurately as can be expected in a survey of this kind.

For comparison it may be of interest to observe the numbers of reported echinococcus cases from the time such reports are available. Figure 1 shows the enormous decline which has taken place in the number of these patients. If we apply Magnússon's method to find out the number of echinococcus cases, we see that their number is only a tenth part in 1940 of what it was in 1912, when he made his estimate, that 1 out of every 240 had an echinococcus. According to his estimate there should be 10 times fewer echinococcus cases now, or 1 in every 2400 inhabitants. As we find an echinococcus in 1 out of 20, the difference is enormous and cannot be explained by the assumption that only 1% of echinococcus carriers can be regarded as patients. In our material 10% of the parasites had been clinically manifest prior to death and certainly a very considerable proportion of dead parasites of orange size must have caused clinical symptoms formerly, which in some cases was evident from the anamnesis.

The explanation of this great discrepancy is simply that even the most experienced and sagacious investigators have not been able to estimate with anything approaching exactness the distribution of hydatid cysts in this country, as long as they had no autopsies on which to base their calculations. The population has been more heavily infested with the parasites than anybody could imagine. Probably a third or even a half of the adult population has harbored an echinococcosus at the close of the last century. We can obtain an idea of the situation by observing the findings in the old people during

the first years of our autopsy work. From 1930 to 1934 we performed autopsies on 32 individuals past 60 years of age. In 11 of these 32 persons, hydatid cysts were found. These people have been about 30 years old at the close of the last century and the parasites were probably all older than that.

poverty was widespread and lack of cleanliness very common. Under these circumstances the parasite had obtained almost ideal conditions for its subsistence. Krabbe[8] found *Tænia echinococcus* in 28% of Icelandic dogs in 1862 and showed that this infestation rate was 47 times higher than in Denmark. Not only were the dogs

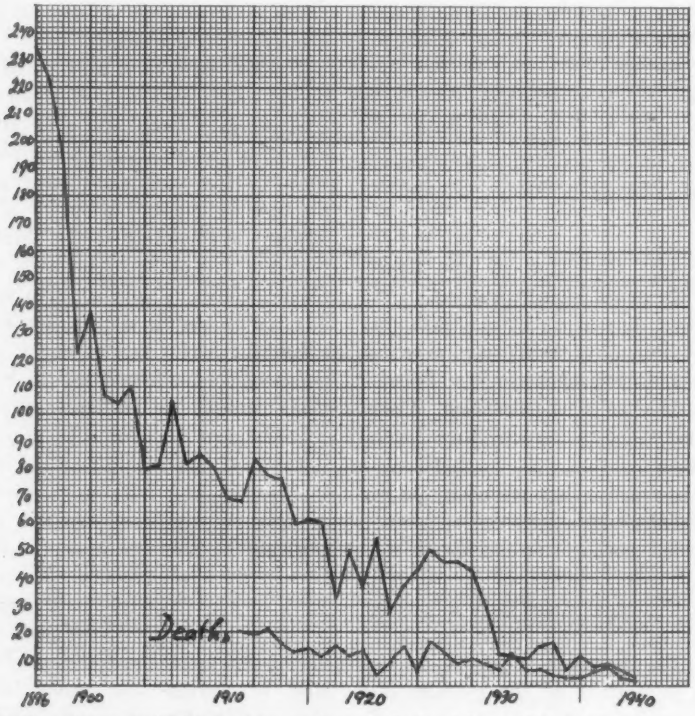

FIG. 1.—Number of reported echinococcus patients in Iceland from 1896–1940 and reported deaths from echinococcosis since 1911.

Discussion. It is evident that echinococcosis has been more widespread here than even the highest estimates supposed. This is not surprising, considering the living conditions of the people, who lived in close communion with dogs and were completely ignorant about the nature and contagiousness of the disease. And this state of ignorance continued through centuries, when the entire population lived under primitive conditions as sheep breeders, when everybody was exposed to contact with dogs and every dog had access to the entrails of sheep. Extreme

highly parasitized, but their number was enormous (15 to 20,000) at a time when the population was only 70,000.

In a medical report 1858 Finsen mentions that an old ewe or a cow is very rarely slaughtered without finding an echinococcus cyst. Probably the condition of the human population would have been found similar, if proper investigations had been made.

There can be little doubt that the young generation now growing up in this country is practically free from echinococcosis, as is borne out by our autopsy records. The

parasites are only harbored by the old people and it is to be expected that the present young generation will show a very low echinococcus rate when its time comes to take the place of the old generation.

The *causes* of this decrease in parasitism are several. First and foremost is the education of the population. The causal relationship between hydatid cysts in people and sheep on the one side and the tænia in the dogs on the other side has been explained to the entire population and even in the children's schools.

Slaughtering of sheep is done under such conditions that dogs have no access to the entrails of sheep.

Every dog in the country is given an anthelminthic once a year. The effect of this measure is seen in the disappearance of all kinds of helminthic cysts in sheep, also the *Cœnurus cerebralis*, which used to be seen more or less in every flock of sheep in the last century.

The further cause of the decrease of parasitism is the change which has taken place in the sheep breeding industry. Formerly sheep were grown until they were 3 to 4 years old before they were killed. By that time their hydatid cysts were old enough to have developed scolices. Now the lambs are killed when 5 months old, but comparatively few old sheep are slaughtered.

One more reason has been added during the last 3 decades: The rural population has moved to the towns and villages, and the fact that one-third of the entire population lives in Reykjavik, greatly diminishes the danger of exposure for that part of the population.

Summary. In a total of 1231 autopsies 60 hydatid cysts were found. The young generation is practically free from this disease which is found with increasing frequency in the higher age groups. The infestation rate among the oldest age groups is a remnant of the old conditions, when the population had been heavily parasitized.

The causes for the improvement in these matters are discussed.

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TRAUMATIC STREPTOCOCCIC MENINGITIS

REPORT OF A CASE WITH RECOVERY AND REVIEW OF LITERATURE*

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SINCE the advent of sulfonamide therapy, and more recently penicillin, reports of successfully treated streptococcic meningitis have become commonplace. Of 102 cases reported from 1935 to 1939, 81 (79.4%) had recovered;[12] whereas prior to present-day chemotherapy the estimated mortality was 97%.[4] Such cases were nearly all of otogenic origin. So-called post-traumatic meningitis, on the other hand, and particularly when secondary to a streptococcus, is exceedingly rare. Thus, careful perusal of the literature[1,2,3,5,6,8,9] reveals only 8 cases cured by means of sulfonamides (Table 2). In contrast only 5 cases were reported cured during the pre-sulfonamide era of 1901–1935 (Table 1).

TABLE 1.—CASES OF TRAUMATIC STREPTOCOCCIC MENINGITIS SUCCESSFULLY TREATED FROM 1901 TO 1935 (PRE-SULFONAMIDE ERA)

Author	Cases	Age	Injury	Organism	Treatment
Barth (1914) . . .	1	19	Back trauma	Streptococcus	Laminectomy
McCarthy *et al.* (1917)	1	25	Head trauma	Streptococcus	Spinal drainage and anti-streptococcic serum
Dandy (1924) . . .	1	6	Head trauma	Streptococcus	Surgical drainage
Canuyt *et al.* (1933) .	1	11	Trauma to eyelid	Streptococcus	Spinal drainage and anti-streptococcic serum
Zeligs (1935) . . .	1	6	Basal fracture	Streptococcus	Spinal drainage and anti-streptococcic serum

The majority of cases of traumatic meningitis encountered in the literature were found to be due to a pneumococcus. Trauma, as a rule, occurred to the head or face with resultant skull fracture in practically all cases. Those in whom a cerebrospinal leak was demonstrated were especially vulnerable to meningeal infection.

Because of the rarity of successfully treated streptococcic meningitis of traumatic origin the following case was considered worthy of adding to the literature. The long incubation period as well as the unusual strain of organism are of interest and may have been factors influencing the favorable outcome of the patient's illness.

Case Report. G. L. R., 31 year old garage attendant, entered the Veterans Hospital, San Francisco, Feb. 15, 1945 (his second admission) with a tentative diagnosis of meningitis. He was first admitted into the hospital on January 15 for treatment of a nasal laceration, 10 days after a fall against a screen door. The laceration had been sutured originally at one of the city emergency hospitals, and had apparently healed by primary intention. The day before his first entry he reinjured his nose, reopening the old laceration. Roentgen ray revealed a comminuted fracture of the nasal bone and it was concluded that the fracture was compounded. The distal fragment was elevated by splints and a secondary closure of the soft tissues was carried out. The wound healed normally and he was discharged from the hospital on February 3. He returned to work and felt well until the day prior to his present (second) admission. At this time he became ill with headache, malaise and low

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back pain. Within the course of the next several hours he became acutely prostrated with chills, fever, nausea, vomiting and stiff neck.

The past history disclosed the following facts: disability discharge from the U. S. Army in 1943 because of duodenal ulcer; malaria in 1931 with relapse in 1932; and renal colic in 1932 with passage of a calculus.

TABLE 2.—CASES OF TRAUMATIC STREPTOCOCCIC MENINGITIS SUCCESSFULLY TREATED BY MEANS OF CHEMOTHERAPY

Author	Cases	Age	Injury	Incubation, days	Organism	Treatment
Frazer (1937)	1	17	Skull fracture	7	Hem. strep.	Prontosil and spinal taps
Davel (1937)	1	16	Skull fracture, cerebrospinal otorrhea	10	Hem. strep.	Prontosil and spinal taps
Ricard *et al.* (1938)	1	?	Basal skull fracture, cerebrospinal rhinorrhea	4	Hem. strep.	Sulfanilamide and polyvalent serum
Narat (1939)	1	52	Skull fracture (through frontal sinus) and nasal fracture	3	Hem. strep.	Sulfanilamide
Gurdjian (1941)	2	14	Basal fracture, cerebrospinal otorrhea	5	Hem. strep.	Sulfanilamide
		29	Basal fracture, aural bleeding	5	Hem. strep.	Sulfanilamide
Boatman (1941)	1	25	Spinal injury by shrapnel	21	Hem. strep.	Laminectomy and prontosil
Riley and Waugh (1943)	1	33	Skull fracture (involving frontal sinus)	2	Non-hem. strep.	Sulfapyridine
Berk (1945)	1	31	Nasal fracture, compound	32	Non-hem. strep.	Sulfadiazine and penicillin

Physical examination revealed an acutely ill, restless, rational white man, who complained of severe headache and low back pain. The neck was rigid and a bilateral Kernig sign was present. Otoscopic examination was negative. Percussion over the entire spine disclosed tenderness. The skin was hot and there was evidence of dehydration. The temperature was 102° F., pulse rate 120, and respiratory rate 24. Blood pressure 110/80. A horseshoe-shaped recently healed scar about 4 inches in length extended across the bridge of the nose. At its mid-point there was some soft tissue thickening but no signs of active inflammation.

A lumbar puncture revealed turbid fluid under 180 mm. initial pressure with a cell count of 8600, nearly all of which were polymorphonuclears. Spinal sugar content was less than 10 mg. per 100 cc., and the protein was 333 mg. per 100 cc. Immediate smears disclosed no organisms. White blood cell count was 8800 (85% neutrophils).

Treatment. The patient was immediately given 5 gm. of sodium sulfadiazine by the intravenous route, and 20,000 units of penicillin intramuscularly. Several hours later the vomiting subsided and he was able to take 1½ gm. of sulfadiazine orally every 4 hours. Penicillin was continued every 3 hours. Approximately 24 hours after admission 10,000 units of penicillin in 10 cc. of saline was injected intrathecally after a like quantity of spinal fluid was removed. A short while later his back pain became aggravated, with radiation down the lower extremities. Morphine was required for relief. After 48 hours, culture of the spinal fluid showed a non-hemolytic streptococcus, which later proved to be micro-aërophilic. Blood culture was negative.

In view of the favorable clinical response at the end of this time and because of the untoward reaction to intrathecal penicillin the day previously, further medication by this route was not deemed advisable. At the end of the 3rd day the patient's temperature had reached normal and his neck rigidity had disappeared. The spinal fluid on the 5th day was clear for the first time with a cell count of only 120, most of which were polymorphonuclears. Dextrose value

was 26 mg. %. Smear and culture of spinal fluid were negative. On the 8th day the spinal cell count was 56, only 24 being polymorphonuclears. The sugar content had risen to 100 mg. %, and the protein value was reported as 48 mg. %. Culture was negative.

Penicillin was discontinued after 5 days, a total of 520,000 units having been administered intramuscularly and 10,000 units intrathecally. Sulfadiazine was continued for 10 days, the patient having received 56 gm.

The patient was discharged as recovered without complication or sequela on March 6, after less than 3 weeks hospitalization. His recovery was attributed primarily to sulfadiazine, owing to the fact that clinical and cultural response had been manifest within the 1st 24 hours of his illness, which was prior to the injection of intrathecal penicillin. The effect derived from the intramuscular penicillin was considered of minimal degree since it has been shown[7] that when administered in this manner it does not pass the meningovascular barrier in significant quantities. On the other hand, although only 1 injection was given intraspinally, its effect probably played no small part in the successful outcome. This conclusion is borne out by Rosenberg and Arling's[10] report of 40 cases of meningitis treated by penicillin in which the majority of patients required only 1 or 2 intrathecal injections.

Comment. The portal of entry of the offending organism in the above case was probably through a defect in the cribriform plate. Schroeder[11] mentions 2 additional sites where a defect is apt to occur in nasal injuries, with resulting communication between the nasal cavity and cerebrospinal system, namely, in the posterior wall of the frontal sinus with a tear in the dura, and defects in the walls of the sphenoid sinus. Trauma to the nose or face may lead to any one of these fistulous communications and thus invite infection of the meninges by an organism which inhabits the nasal passages at the time.

Of the 8 tabulated cases, 7 suffered a head injury with skull fracture in all but 1. Two patients had in addition fractures involving the frontal sinuses, which may have been the portal of entry. Three cases with basal fractures presented cerebrospinal otorrhea, whereas a fourth suffered bleeding from the ear. Thus, one may conclude otitic origin of infection in the latter 4 cases. Boatman's patient was the only one whose meningitis originated in an injury below the head. The author's case, on the other hand, is the only one secondary to an uncomplicated nasal injury.

Summary. 1. A case of traumatic streptococcic meningitis, secondary to a compound nasal fracture, and successfully treated with sulfadiazine and penicillin is hereby presented.

2. Only 8 cases of traumatic streptococcic meningitis cured by chemotherapy are found in the literature, to which a ninth is added by the author.

3. The author's case is the first reported due to a non-hemolytic (micro-aërophilic) streptococcus and cured by chemotherapy.

4. Prophylactic sulfonamide and penicillin should be given in all cases of traumatic cerebrospinal fluid leaks.

5. Traumatic meningitis due to pneumococcus occurs more frequently than meningitis due to streptococcus. This might be explained by the predominance of the former organisms in the nasal and aural passages.

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PNEUMONITIS OCCURRING IN RHEUMATIC FEVER

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Pneumonitis occurring in the course of rheumatic fever is one of the more prominent of the protean manifestations of rheumatic fever. American and English writers have spoken of the rheumatic pneumonias and described in part the clinical picture. Fuller[3] and Garrod[4] described rheumatic pleurisy as part of the rheumatic fever entity. Fuller has written of the frequency of the occurrence of pneumonias in acute rheumatic fever. Garrod mentioned the transient character of the physical signs. In recent years Thayer[8] and Swift[7] described the clinical picture and noted the frequency of rheumatic pneumonitis and pleurisy. In 1928, Paul[6] presented a very complete historical review and outlined the physical findings in detail. In 1928, Gouley and Eiman[2] described the gross and histologic pathologic findings, and based their opinion of the specific nature of rheumatic pneumonitis upon "the histologic study of the lungs showed an acute interstitial inflammatory process, apparently hematogenous in origin, with hyperemia, edema and a characteristic cellular exudate, perivascular, consisting of large endothelial cells, giant cells, plasmocytes, lymphocytes and a few neutrophils, the distribution of this exudate and its general appearance being identical with the cardiac lesions in rheumatic fever and occurring in such a case." In 1932, Gouley and Eiman[1] again published their findings in the lungs in 9 cases of acute rheumatic fever. They were similar to the description quoted above.

Definition. Pneumonitis is a manifestation of rheumatic fever characterized by an inflammatory process of the lung and pleura, with an insidious onset, migrating consolidation, and frequent pleurisy with or without effusion.

Source of Material. In a group of 1046 rheumatic fever patients observed in the rheumatic fever unit at the U. S. Naval Hospital, pneumonitis was found in 119 cases.

Table 1.—Occurrence Rate of Pneumonitis

Type	No. patients with rheumatic fever	No patients developed pneumonitis	%
Acute fulminating	52	28	53.1
Polycyclic	281	77	27.4
Monocyclic, subacute	667	14	2.0
Subclinical	46	None	0.0
Total	1046	119	11.3

Occurrence. The occurrence rate in this group of patients was 11.3%. Table 1 shows that the most frequent occurrence was in the acute and polycyclic types of the disease. No demonstrable pneumonitis was found in the subclinical types.

Pathologic Anatomy. The gross and histologic pathology are discussed in detail in recent papers by Huntington and the author.[5] In short, gross examination shows areas of mottling which are characteristic of infarction. The cut surface is smooth and, although hyperemic in appearance, is relatively bloodless. The mottled areas may be found in all lobes of the lungs. The histologic picture is

that of an anaphylactic angiitis involving the larger vessels as well as the capillaries. There is endothelial proliferation, hemorrhage, necrosis and hyalinization. Perivascular infiltration of plasmocytes, giant cells, lymphocytes, myocytes with owl-eyed nuclei and relatively few neutrophils there is little residual evidence of the pleuritis. An effusion is found relatively infrequently. In this series of cases effusion occurred in 10.9% of the cases. Effusions tend to be temporary. The fluid is sterile and straw to sanguinous in color, depending upon the number of red

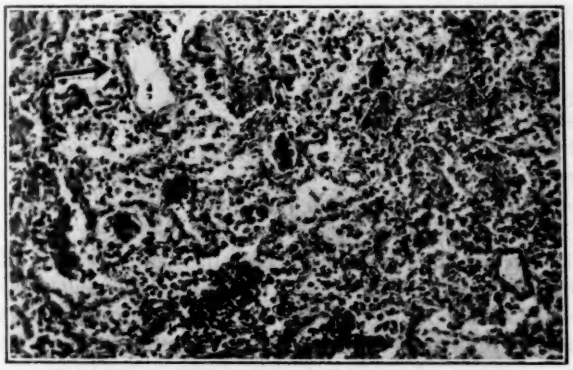

FIG. 1.—Lung. Pneumonia with alveolar exudate made up mostly of fibrin, large monocytes and lymphocytes. Note the amorphous "hyaline" character of some of the acellular material. The blood vessel marked by the arrow is involved, apparently, in the inflammatory process.

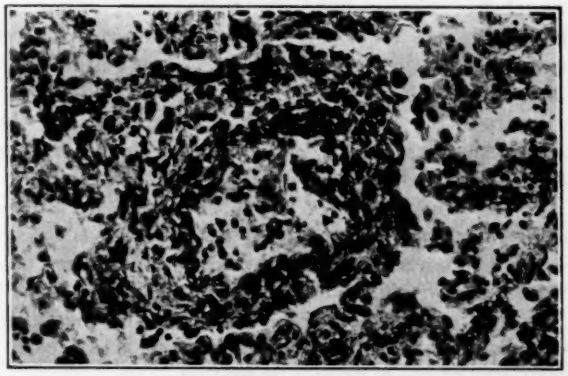

FIG. 2.—Inflammatory reaction in small artery in lung. (Autopsy 3), H. & E.

Figures 1 and 2 were photographed by Dr. R. W. Cragg at the U. S. Naval Medical School. The remaining figures are the work of Mr. Edward N. Hamilton at the College of Medical Evangelists, Los Angeles.

is characteristic. Aschoff bodies may be found freely in various stages of development and maturity. The alveoli are filled with collagen, fibrin and blood cells. The pleura may show a fibrinous exudate on both the parietal and visceral membranes. Organization and formation of fibrous adhesions may occur, but more frequently cells. At times large numbers of eosinophils are found in the white cell count. The effusion may absorb very rapidly with very little residual evidence of the pleurisy.

Types of Pneumonitis. There are 3 clinical types of pneumonitis recognizable: (1) primary acute pneumonitis, (2) secon-

dary acute pneumonitis, and (3) subclinical pneumonitis.

1. *Primary acute pneumonitis* may be and is at times the presenting manifestation of rheumatic fever. The history of an upper respiratory infection several weeks previously, a period of latency, the development of shortness of breath on exertion, cough, occasional blood spitting, fever of moderate to high degree, tachycardia of greater degree than that usually found with the height of the temperature, cyanosis and restlessness are the symptoms and signs by which this manifestation may be suspected. On physical examination an area of dullness may be found in 1 or more lobes, accompanied by a suppression of the breath sounds and a few fine, crackling râles. This area may develop into frank consolidation with increased dullness and tubular breathing. More frequently, however, the original area clears in 2 to 3 days and a new area develops. After 2 or 3 days other manifestations of rheumatic fever appear, such as migrating polyarthritis, carditis and a sustained relatively high fever. The diagnosis is confirmed by finding an area of cloudiness in 1 or more lobes of the lungs from Roentgen ray study. There is a leukocytosis of moderate degree, without a marked shift to the left in the Schilling index. The sputum study usually shows no pathogenic organisms and is relatively free of leukocytes. The sedimentation rate is usually high, and at times there is electrocardiographic evidence of myocardial change. The course of the primary acute type of pneumonitis is severe and prolonged. The pneumonitis may become so widespread as to cause a very greatly decreased oxygen carbon dioxide exchange, with marked cyanosis and air hunger. At the same time the pulmonary arterial tension rises to such a level that there may be primary right-sided heart failure. The heart which is the seat of a severe carditis is unable to meet the increased work load thrown on the right ventricle, and primary right ventricular failure may ensue. It is the opinion of the clinicians working in this group that where there is primary right-sided heart failure in rheumatic fever, pneumonitis is one of the initiating causes. The pneumonitis subsides only as the other manifestations of the rheumatic fever subside. The physical signs of the pneumonitis clear up long before the Roentgen ray findings become negative.

Table 1 shows that 53.1% of the acute fulminating type of rheumatic fever had rheumatic pneumonitis and in approximately one-half of these cases the initial symptoms were referable to the lungs. Most of the patients were treated for a primary atypical pneumonia until other manifestations of rheumatic fever appeared, such as polyarthritis and carditis.

2. *Secondary acute pneumonitis* occurs during the course of established rheumatic fever. From Table 1 it is noted that secondary acute pneumonitis occurs most frequently in the polycyclic type of rheumatic fever. The actual occurrence rate was 27.4%. The onset may begin late in the first cycle, but more frequently it is one of the presenting manifestations of the second or third cycle of the polycyclic type.

The symptoms are those of shortness of breath, cough, pain and restlessness. Cough may be primary and severe, or mild to absent. Pain is usually late in its appearance as a symptom, but is severe and prolonged unless an effusion develops. Cyanosis is present only if involvement of the lungs is widespread. Restlessness is an early and persistent symptom.

The first signs to appear are fever and tachycardia. Dullness over localized areas of the lungs appears early and may shift from 1 lobe to another or within the same lobe. The dullness may increase to flatness with the development of massive involvement of a lobe or with the rapid pouring out of a pleural effusion. Early the breath sounds are diminished over the area of dullness. As the area of involvement increases, tubular breathing may develop but this is relatively infre-

quent. Râles at first are small and finely crackling. Later the râles increase in number and become more moist in nature. The signs may clear fairly rapidly, but they may, however, persist as long as other manifestations are present. The Roentgen ray study confirms the diagnosis by revealing an area of cloudiness at the site of the physical findings. The fever, tachycardia, the leukocytosis and blood sedimentation rate are elevated usually in proportion to the severity of the rheumatic process.

Roentgen Ray Findings. The characteristic findings in the Roentgen ray studies in rheumatic pneumonitis and pleuritis are the rapid onset and clearance of densities in one area to suddenly reappear in another area in the lung fields, and the equal rapidity with which a pleural effusion may appear and then as quickly disappear, and the close association of the pneumonic densities to the bronchovascular markings spreading into the adjacent parenchyma. At the onset the area of cloudiness is similar to that

TABLE 2.—PNEUMONITIS—LOBES INVOLVED

Location	No of cases
Central hilar area	16
Middle lobe	11
Upper lobes	18
Basal lobes	26
Multiple lobes	48
Total	119

FIG. 3.—Thrombus (*A*) with beginning recanalization (*B*) in medium-sized pulmonary artery, arterial wall is (*C*). (Autopsy 6.) Masson Trichrome, × 125.

3. *Subclinical pneumonitis* is found accidentally. There are no symptoms and few, if any, physical signs. The subclinical pneumonitis is suspected when a rheumatic fever patient is more ill than the clinical findings would indicate. The diagnosis is based entirely on the Roentgen ray finding of an area of cloudiness either in the hilar area or in isolated fields of the lungs (see Table 1). Subclinical pneumonitis of rheumatic origin occurred in 2% of the subacute monocyclic cases.

seen in primary atypical pneumonia and that seen in sulfonilamide sensitivity. There is localized patchy density without much shift of the mediastinum. At times the area of cloudiness may be triangular and near the periphery, resembling an infarction; and again it may be circular and central. Table 2 shows the distribution of pneumonitis according to lobes involved. Multiple and upper lobe involvement occurred more frequently in the very ill patients.

Pleurisy was not found as frequently as

the early writers indicated. Most of the cases of pleurisy were confirmed by Roentgen ray findings. Effusion accompanying pleuritis is not infrequent, occurring in 18.8% of cases of demonstrable pleurisy. The percentage of occurrence of pleuritis would be much higher if pain is taken as the diagnostic criterion. To make the diagnosis of pleurisy, pain, pleural friction rub and positive Roentgen ray findings of thickened pleura, peripheral pneumonitis and/or effusion were required.

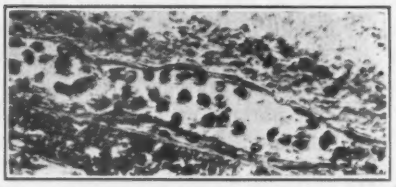

FIG. 4.—Small pulmonary vessel (Autopsy 6), showing edema and cellular accumulation beneath inner layer. Masson Trichrome, × 500.

Bacterial pneumonia is differentiated by the sudden onset with chill, high fever, characteristic sputum, Roentgen ray findings of lobar involvement, and the laboratory determination of the causal organism.

Tuberculous pneumonia is differentiated by the history of exposure, by the course of the pneumonia and the absence of the protean manifestation of an active rheumatic state.

Pleurisy with effusion cannot be differentiated except by guinea-pig inoculation. The development of carditis, migrating polyarthritis, erythema marginatum and subcutaneous nodules aid in the differential diagnosis pointing to rheumatic fever rather than to tuberculosis.

FIG. 5.—Fibrinous and cellular exudate in lung. Rupture of capillary at arrow. (Autopsy 6.) Masson Trichrome, × 125.

FIG. 6.—Lung. Showing border of infarcted area (Case 6). × 80.

Differential Diagnosis. The differential diagnosis is not easy. The primary acute pneumonitis cannot be distinguished from primary atypical pneumonia either clinically, by the sputum studies, by Roentgen ray, or by blood studies. The pneumonitis of rheumatic fever is recognized when the other manifestations of rheumatic fever appear. The concomitant manifestations which are most helpful in establishing the diagnosis of rheumatic pneumonitis are carditis, migrating polyarthritis, purpura, erythema marginatum, epistaxis and subcutaneous nodules.

The differentiation of rheumatic pneumonitis from congestive heart failure is based upon the following facts. In congestive heart failure air hunger and increased venous pressure are more marked. In congestive failure there is an enlarged liver which is tender and pulsates. Ascites and dependent edema soon follow. A tri-

cuspid systolic murmur is frequently heard. Since pneumonitis frequently precedes congestive failure, careful observation and timing of events is necessary to state where the pneumonitis is complicated by congestive failure.

with a moderate increase in the granulocytes in all types of lung involvement except the primary atypical pneumonia. The antistreptolysin titer is definitely elevated in rheumatic fever, with or without a pneumonitis, and serves to

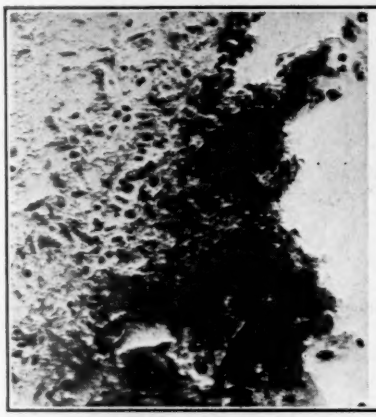

FIG. 7.—Vegetation in large branch of pulmonary artery (Case 8). Masson Trichrome, × 320.

FIG. 8.—Pleural surface (arrow) with group of mononuclear cells. Subpleural group of dilated vessels (Case 8). Masson Trichrome, × 160.

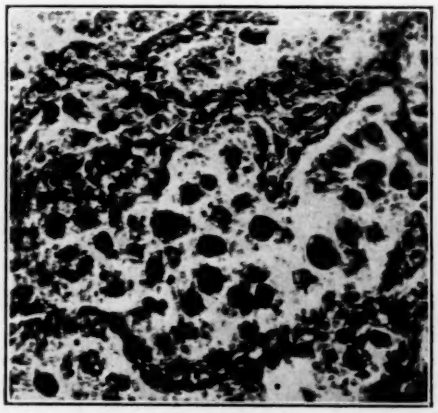

FIG. 9.—Alveolus, showing cellular detail (Case 8). Masson Trichrome, × 320.

The laboratory aids are of little help in the differential diagnosis except in lobar pneumonia. The blood sedimentation rate is elevated approximately to the same level in primary atypical pneumonia, in tuberculous pneumonia and in rheumatic pneumonitis. The leukocyte count is elevated as high as 20,000 to 25,000 cells, differentiate rheumatic pneumonitis from the primary atypical pneumonia, bacterial pneumonia and from tuberculosis.

Discussion and Conclusions. 1. Pneumonitis is one of the prominent manifestations of rheumatic fever activity.

2. Pneumonitis is a definite pathologic entity only when considered as one of the

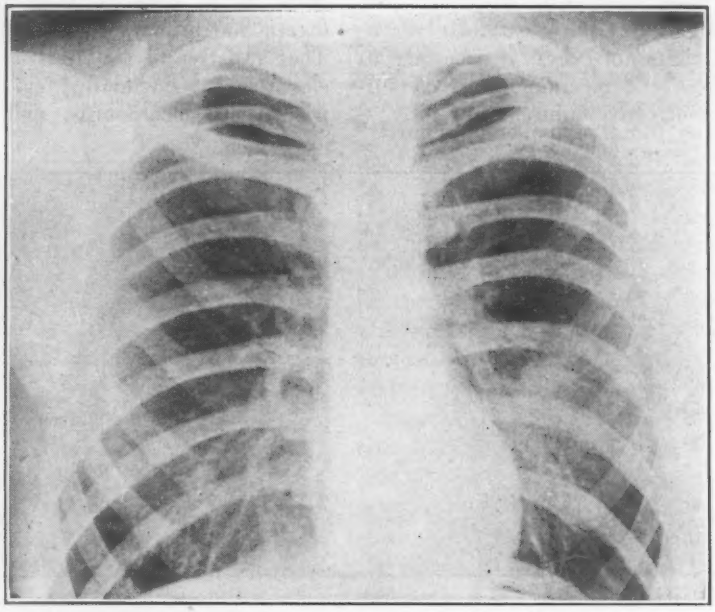

FIG. 10.—Case 1, No. 15328. Rheumatic pneumonitis. Radiograph of the chest reveals a diffuse patch of increased density at the level of the third left anterior interspace.

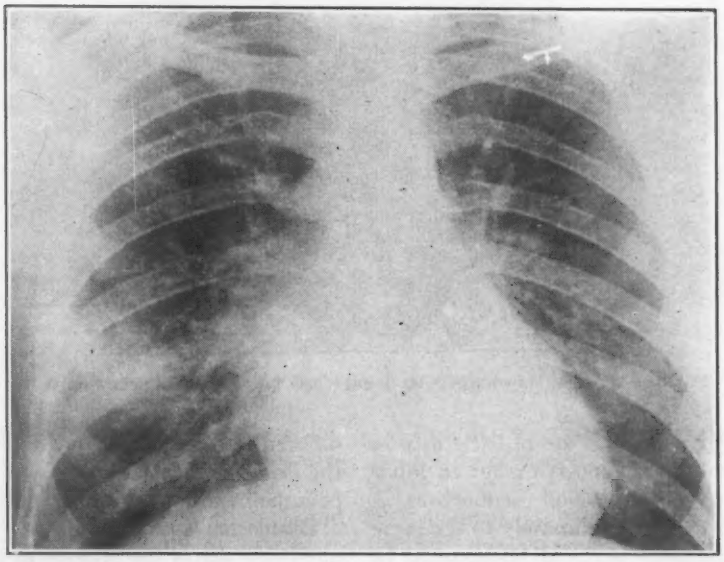

FIG. 11.—Case 2, No. 8443. Rheumatic pneumonitis with associated pleural changes. Radiograph of the chest reveals a patch of increased density at the level of the fourth and fifth right anterior interspaces. There is associated haziness about this area consistent with pleural changes.

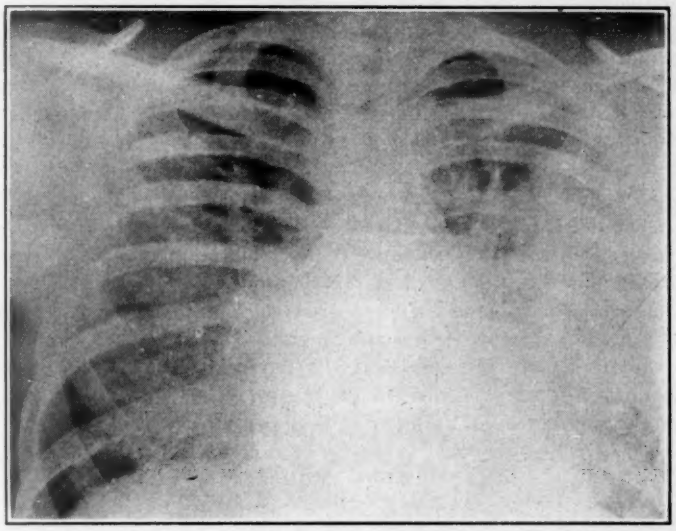

FIG. 12.—Case 3 (radiograph No. 1), No. 18849. Rheumatic pneumonitis. Radiograph of the chest reveals multiple patches of increased densities throughout both lung fields.

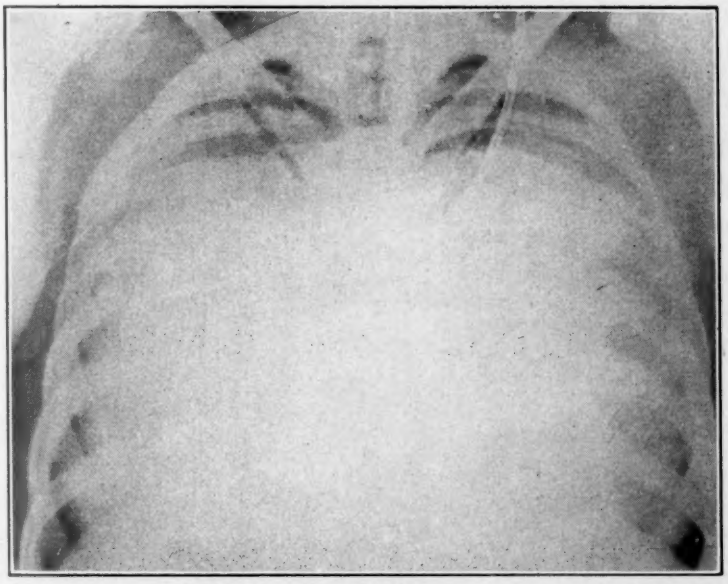

FIG. 13.—Case 3 (radiograph No. 2), No. 18849. Rheumatic pneumonitis and terminal pulmonary congestion. Radiograph of the chest 3 days following previous radiograph now reveals diffuse homogeneous densities throughout the inner and middle zones of both lung fields.

manifestations in the widespread angiitis of rheumatic fever.

3. Pneumonitis occurs in approximately 11% of rheumatic fever cases. It is seen in 53.1% of the acute fulminating type; in 27.4% of the polycyclic type, and in 2% of the mild monocyclic type of rheumatic fever.

4. The pneumonitis is of 3 types, according to its time of appearance in the rheumatic fever state: primary acute, secondary acute, and the subclinical.

5. The diagnosis of pneumonitis of rheumatic origin is based entirely on the exclusion of the other types of pneumonia and the concomitant development of other manifestations of acute rheumatic fever.

6. Roentgen ray findings in pneumonitis of the rheumatic type are not specific; but the rapid shift of areas of density, the rapid development of an effusion and the close adherence of the density to the bronchovascular markings are helpful findings.

7. There is no specific laboratory test. The laboratory aids are of little help in establishing the diagnosis.

8. The importance of pneumonitis of rheumatic fever origin as one of the serious manifestations of rheumatic fever activity cannot be overemphasized.

Summary. A study of 119 cases of pneumonitis, with histologic and Roentgen ray illustrations is presented.

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SELECTION OF PATIENTS WITH ARTERIAL HYPERTENSION FOR TREATMENT BY REPEATED INJECTIONS OF PITRESSIN

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In 1941 Griffith, Corbit, Rutherford and Lindauer[1] described a group of patients with high blood pressure whose sera contained a substance capable of suppressing water diuresis in rats. It was suggested that this antidiuretic substance was, in fact, the antidiuretic hormone derived from the posterior lobe of the pituitary, and that the hypertension in these patients was due to increased activity of the posterior lobe of the pituitary. Subsequently, Pendergrass, Hodes and Griffith[4] and later Pendergrass, Griffith, Padis and Barden[5] described the result of treatment of such cases by pituitary irradiation. About half the patients so treated showed a drop in blood pressure, frequently to the normal range, along with clinical improvement, both occurring 1 to 3 months after the irradiation and associated with disappearance of the antidiuretic substance from the blood stream.

In 1940 Robinson and Farr[6] described a treatment for patients with edema, by repeated injections of aqueous pitressin. They found that such injections, if given daily, would increase the antidiuretic titer of the urine for a few days, but subsequently the urine would become actually diuretic as compared with its pre-injection level. They suggested that this effect was due to the appearance in the body of an antagonist to pitressin, and showed that, at the time when it appeared, edema was usually cleared. It is possible that the explanation may be the development of an antihormone, but this has not yet been established.

It seemed probable that repeated injections of pitressin might have an effect such as had previously been observed following irradiation. In the beginning small doses of the aqueous preparation were used varying from 0.2 to 1 cc. (Pitressin, Park Davis, each cc. containing 20 pressor units). Patients were selected on the same basis as for pituitary irradiation, as follows: (1) Bio-assay for antidiuretic hormone in serum must be positive; (2) bio-assay for gonadotropic hormone in serum must be negative at the level of 330 mouse units per 100 cc. (the method used was that described by Rakoff[7]); (3) renal function must be normal as tested by the plasma creatinine method described by Steinitz and Turkand.[8] In addition, patients were selected who were less than 60 years of age who had suffered no previous vascular accident. They were also studied from the standpoint of capillary reactivity by the method described by Griffith, Roberts and Corbit,[2] and cutaneous lymphatic flow by the patent blue method of McMaster,[3] although neither of these tests was used in actual selection. Subsequently pitressin tannate in oil became available (Park Davis, 1 cc. = 5 pressor units) and this was substituted for the aqueous preparation.

Material and Method of Study. In all, 63 patients with arterial hypertension were studied, treated, and followed for a period varying from 3 to 26 months, averaging 8 months; 33 of these were males, and 30 females. Ages ranged from the 2nd to the 6th decade, with only 5 subjects below 30.

* Atwater Kent Fellow in Medicine.

TABLE 1.—EFFECT OF INJECTIONS OF PITRESSIN UPON BLOOD PRESSURE

Systolic blood pressure after injections	A. Systolic blood pressure before injections: 200–250	170–200	150–170	Below 150
200–250	5			
170–200	4	16		
150–170	(3)	11	9	
Below 150	(1)	(4)	(10)	

Diastolic blood pressure after injections	B. Diastolic blood pressure before injections: Over 140	120–140	110–120	100–110	Below 100
Over 140	1				
120–140		7			
110–120		4	9		
100–110		(3)	6	5	
Below 100		(3)	(7)	(7)	11

Numbers refer to number of patients. Those in parentheses are thought to show good results and those in bold face fair results.

TABLE 2.—CORRELATION BETWEEN CHANGE IN SYSTOLIC AND IN DIASTOLIC BLOOD PRESSURE FOLLOWING INJECTIONS OF PITRESSIN*

Diastolic blood pressure change	Systolic blood pressure change: Good	Fair	No change
Good	11	8	1
Fair	1	6	2
No change			23

* The 11 patients whose initial diastolic blood pressure was below 100 are omitted from this correlation. Of these the systolic change was good in 6 cases and no change in 5.

TABLE 3.—CORRELATION BETWEEN CHANGE IN SYSTOLIC BLOOD PRESSURE AND CLINICAL IMPROVEMENT

Clinically	Systolic blood pressure change: Good	Fair	No change
Good	10	6	
Probably good	8	5	7
No change		4	23

TABLE 4.—FACTORS INFLUENCING THE RESPONSE TO INJECTIONS OF PITRESSIN TANNATE IN OIL IN HYPERTENSION

Group:	1 Clinical and blood pressure good	2 Clinical good, blood pressure fair	3 Clinical probably good, blood pressure good	4 Clinical probably good, blood pressure fair	5 Clinical probably good, blood pressure no change	6 Clinical no change, blood pressure fair	7 Clinical and blood pressure no change
After injections, bio-assay antidiuretic hormone:							
Negative	10	5	8	5	5	3	11
Positive	..	1	..	..	2	1	12
Pitressin:							
(a) Aqueous	1	..	4	..	1	..	7
(b) In oil:							
Less than 6 injections	..	..	..	..	1	..	9
More than 6 injections	9	6	4	5	5	4	7
Before treatment cutaneous lymphatic flow:							
Normal	6	3	5	3	5	1	5
Increased	3	3	2	2	2	3	10
Before treatment cutaneous capillary reactions:							
Normal	10	5	4	3	6	4	18
Abnormal	..	1	1	2	1	..	3

Treatment may be divided into 3 general types: (1) 13 patients were given injections of aqueous pitressin in the dose previously stated, daily, for 6 injections or more; (2) 10 persons were given intramuscular injections of pitressin tannate in oil, each 1 cc., at weekly or monthly intervals, the total number of injections being less than 6; (3) 40 persons were treated similarly, but received 6 or more injections. The usual procedure was to begin with 3 injections at weekly intervals, and follow by 3 or more injections at monthly intervals, until the bio-assay for antidiuretic hormone became negative. In the beginning and for the first 3 to 6 months, bio-assays were repeated at monthly intervals; thereafter, as far as possible, every 3 months.

Results. Table 1 shows the effect upon systolic and diastolic blood pressure. There was a significant reduction in pressure in about half the subjects treated, and this at times was marked. Correlation between change in systolic and in diastolic pressure (Table 2) is good. Moreover, in Table 3, there is a good correlation between clinical result and change in systolic blood pressure. As seen in Table 3, there are 9 possible combinations of change in blood pressure along with clinical change: actually only 7 of these occurred, and these comprise the 7 groups shown in Table 4, where the best results are at the left (Group 1, etc.) and the worst at the right. However, it should be noticed that Group 7 is the only one where we are certain no benefit has been achieved. In the future, one would prefer either not to treat the patients that fall in this group, or else treat them differently. Further study of Table 4 shows that the majority of cases in Group 7 (12 out of 23) failed to show a change in bio-assay for antidiuretic hormone following therapy. It is also apparent that results were better in those patients who received 6 or more injections of the pitressin tannate in oil than in those receiving fewer injections, or in those given the injections of aqueous pitressin. Results were not significantly influenced by the state of the cutaneous capillaries or the rapidity of the cutaneous lymphatic flow.

Immediate reactions to the injections of pitressin tannate in oil did not occur, although 2 patients developed a mild transient urticaria a few hours after an injection. Immediate reactions did occur following injections of aqueous pitressin, even in small dosage, consisting of blanching of the face, a sense of coldness and a vague sensation of being ill, and, frequently, increased peristalsis followed by 1 or more stools. The use of the aqueous preparation has been discontinued and is, in our opinion, not now justified.

Case Report. A housewife, age 47, presented herself on 2-25-44 because high blood pressure had been discovered 3 months previously at the time of a surgical operation for repair of a broken jaw. Readings had been obtained frequently during this period, and ranged from 170/110 to 230/140, more often at the higher than at the lower limit of the range. Patient complained of marked dizziness as her only symptom.

At the time of her initial study, blood pressure was 200/120, bio-assay for antidiuretic hormone was positive, bio-assay for gonadotropic hormone was negative at 330 mouse units, plasma creatinine was normal, cutaneous capillary reactions were normal as was cutaneous lymphatic flow. Pitressin tannate in oil, 1 cc., was injected intramuscularly on 3-28-44, 4-5-44, 4-12-44, 5-5-44, 6-6-44, 7-10-44, and again on 11-11-44. Blood pressure was measured on the following dates, after beginning therapy: 4-5-44 = 166/108; 4-12-44 = 144/104; 5-5-44 = 162/100; 6-6-44 = 150/98; 7-10-44 = 154/104; 9-9-44 = 170/120; 11-11-44 = 138/98; 1-13-45 = 110/70; 4-7-45 = 132/80. Bio-assay for antidiuretic hormone was repeated and was positive on 5-5-44, 6-6-44, 7-10-44, but was negative on 9-9-44 and remained negative thereafter on 11-11-44, 1-13-45, and 4-7-45. All dizziness had disappeared by 5-5-44. Patient moved to a distant city and was not followed further, but reports from her physician stated, as of 9-15-45, blood pressure had remained normal.

Summary. Sixty-three persons with hypertension were selected on the basis of: (1) Positive bio-assay for antidiuretic hormone in serum; (2) negative bio-assay for gonadotropic hormone in serum at the level of 330 mouse units; (3) normal renal function. They were given injections of pitressin tannate using various procedures but the one that appeared best was to give 1 cc. of pitressin tannate in oil weekly for

3 weeks and then monthly for 3 months, and thereafter continuing at monthly intervals until the bio-assay for antidiuretic hormone became and remained negative. Considering the group as a whole, blood pressure was significantly lowered and symptoms improved in about half the cases. Reactions other than occasional mild urticaria did not occur using the procedure just described, but severe reactions did occur when aqueous pitressin was used. The possible mechanism of the reaction is discussed on the basis of the work of Robinson and Farr,[6] and it is suggested the results parallel closely those obtained by pituitary irradiation.

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REACTIONS TO INTRAVENOUSLY ADMINISTERED AMINO ACIDS (CASEIN HYDROLYSATES)

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Parenteral feeding of mixtures of amino acids and lower peptides has become a recognized therapeutic procedure in conditions associated with low nitrogen intake or high nitrogen loss. Most of these mixtures are now prepared by hydrolysis from casein and adjusted so as to contain in sufficient amounts all amino acids essential for maintenance of nitrogen equilibrium, growth and plasma protein production. Hydrolysates of the types now commercially available contain, of course, in addition considerable amounts of "non-essential" amino acids. Table 1 lists the contents of essential amino acids of 2 commercial preparations as compared with the minimum requirements given for rats by Rose.[29] Minimum requirements for man have not been definitely established. No detailed information is at present available as to the content of the remaining amino acids in these mixtures, which presumably approximate that of casein itself.

Table 1.—"Essential Amino Acids" in Casein and Casein Digests (%)

Amino acid	Requirements for rats (Rose)	Casein S*	Casein B.B†	"Parenamine"†	"Amigen"‡
Lysine	1.0	6.3	7.5	8.2	5.8
Leucine	0.8	9.7	12.1	10.6	13.5
Phenylalanine	0.7 (dl)	7.9	5.2	3.6	5.6
Valine	0.7	4.0	7.0	7.3	5.0
Threonine	0.5	3.3	3.9	2.9	4.5
Methionine	0.6 (dl)	..	3.5	3.6	3.0
Isoleucine	0.5	2.5	6.5	6.1	4.8
Histidine	0.4 (dl)	3.8	2.5	1.6	2.0
Arginine	0.2	1.2	4.1	3.8	5.5
Tryptophane	0.2 (dl)	2.2	1.2	1.0 (dl)	1.0

* Data given by C. L. A. Schmidt.[32]
† B.B. data given by Block and Bolling.[2]
‡ Data supplied by manufacturer.
Amino acids marked (dl) are present in their racemic form.

Mixtures of crystalline amino acids, particularly those not containing glycine, glutamic acid, and aspartic acid can be rapidly administered in large amounts while the administration of casein hydrolysates may be followed by undesirable reactions. Few of these have been serious, but recently an instance of fatal reaction to a casein-pork pancreas hydrolysate has been reported.[6] Reactions were common with earlier preparations and have been ascribed in part to the manufacturing process.[5,9,18] Therefore, a reinvestigation of the tolerance of amino acid mixtures prepared with newer methods appeared to be indicated.

The following report discusses the reactions which occurred in the course of intravenous administration of an acid hydrolysate of casein ("parenamine") which when fortified with tryptophane contains all amino acids present in casein. The manufacturing process of parenamine has been changed in recent years[30] and

* The study was supported by a grant made to Eloise Hospital by the Frederick Stearns & Co., Detroit, Michigan.

conclusions drawn from observations previously reported are not necessarily applicable to the present mixture. The solution was administered for the express purpose of determining possible hazards inherent in their therapeutic use.

Method. All solutions used were tested before for pyrogenic activity in rabbits, and were found free of such contaminants.* Amino acids from 149 factory lots were tested and care was taken to avoid contamination of the final solutions. The rubber caps of 2 bottles of the 15% mixture supplied by the manufacturer were removed without touching the glass rim of the bottle. In a similar manner a flask containing 500 ml. of 5% glucose in saline, 5% glucose in water or normal saline was opened and 25 or 50 ml. of the amino acid solution were transferred from each of the bottles into the flask. Usually, the total fluid volume was adjusted to 500 ml. by pouring out some of the dilution fluid before the amino acids were added. Occasionally other concentrations were made in a comparable manner. The final concentration of amino acids varied from 1.5% to 7%, 4% being isotonic.[30] As only the immediate reaction to amino acids was of interest the type of dilution fluid was of no importance. The usual practice of giving large amounts of glucose simultaneously to avoid excessive neoglycogenesis[3] was therefore not always followed. The final mixture contained amino acids from 2 different bottles of the same lot, occasionally from 2 bottles of 2 different lots.

Patients were chosen at random from various services of the hospital, the only prerequisite being the absence of any fever for at least 5 days prior to the testing. Some exceptions are noted below. The infusions were started after a base line for temperature, pulse and respiration had been established. The patients were checked at ½-hourly and hourly intervals for 4 or 5 hours after the end of the infusion or until any reaction had completely subsided. With few exceptions all patients received 2 infusions, 1 containing 50 ml. (7.5 gm.) and 1 100 ml. (15 gm.) of the original mixture. The same lot at the same concentration was always given to at least 2 individuals simultaneously. Therefore, reactions occurring in only 1 of the simultaneously tested patients could reasonably not be ascribed to the amino acid mixture itself. However, if such a reaction did occur, series of similar concentrations from the same lot were further tested in other individuals. One lot was, therefore, tested on from 2 to 6 individuals before judgment as to its purity was passed.

The speed of the infusion was adjusted so that 500 ml. of fluid were delivered in from 45 to 90 minutes (average, 60 minutes). This proved difficult at times and occasionally an infusion would be completed in less than 30 minutes or in more than 2 hours.

In a limited number of cases blood amino acid levels were determined before, during and after the infusion. A micro-method for determination of capillary amino acid nitrogen was used, based on the color reaction of amino nitrogen with naphtho-quinone sulfonate as described by Folin and modified by Sayhun and by Krauel.[20] Values taken on normal subjects 2 hours after a light breakfast ranged from 7.1 to 8.7 mg. per 100 ml. (mean 7.7). These figures are higher than those obtained by others using the ninhydrin method.[36,38] The difference is explained by the fact that whole blood rather than plasma was used. In addition the naphtho-quinone method does not measure amino acids alone. In fact, compounds other than amino acids may react with quinone to a certain extent.[14] Such considerations, however, were thought to be immaterial as the object of the investigation was merely to measure rough changes over a relatively short period of time in fasting patients after a known amount of amino acids had been added to their blood.

Results. Five hundred and fifty infusions were given to 303 patients. As seen from Table 2, 22 reactions were observed in 21 patients, that is, 7% of all subjects experienced a reaction of some kind (4% of all infusions given). In 4 patients (1.3%) the infusion had to be discontinued because of the severity of the reaction. No reaction, however, was alarming or was followed by long-standing or permanent changes.

Table 2 shows clearly that the first

* The data on pyrogen tests were kindly supplied by Dr. C. W. Geiter, Frederick Stearns & Co., Detroit, Michigan.

2 types of reactions which occurred in 8 cases, namely, fever with or without chills, may be grouped together. There is no striking difference in the final amino acid concentration given or in the average infusion time. Such febrile reactions occurred in 1.5% of all infusions and constituted 36% of all reactions encountered. In a number of instances, such reactions could be traced directly to accidental contamination of the infusion set.

In the second patient tested simultaneously and with the same mixture, a temperature rise to 99.6° F. was noted 4 hours after the end of the infusion. No chill occurred. When the final mixture for these 2 patients had been prepared it was left standing in a warm and well-lighted room for over 2 hours before the infusion was started. The same lot was retested in 1 of the 2 patients and in 2 other individuals and no reactions were encountered.

TABLE 2.—22 REACTIONS ENCOUNTERED DURING 550 INFUSIONS OF AMINO ACIDS (PARENAMINE)

Symptoms	No. cases	Average infusion time (min.)	Average amino acid concentration (%)	% of all reactions encountered	% of all infusions
Chills and fever	4	53	3.6	18	0.7
Fever without chills	4	55	2.4	18	0.7
Nausea with or without vomiting and hot flashes	8	36*	3.0	36	1.5
Severe headache	2	..	3.0	9	0.4
Precordial pressure	1	50	3.0	5	0.2
Lumbar pain	1	40	1.5	5	0.2
Dyspnea	2	67	4.0	9	0.4
Total	22	..	..	100	4.1

* One patient suffered from nausea without vomiting the 1st day (infusion time 130 minutes; not calculated in this table) and severe headache the 2nd day. (See text.)

A patient with bronchogenic carcinoma and extensive atelectasis showed a rise in temperature from 99° to 104° after an injection of 500 ml. of 1.5% solution in 20 minutes. Four other patients tested with the same lot had no reaction. It was noted in this case that due to some irregularities in setting up the solution the needle adapter was handled manually in a manner which made secondary contamination possible. Considerable handling of the adapter of the infusion set due to a plugged needle was necessary in another patient who experienced a sudden chill with a rise of temperature to 102° F. after injection of 200 ml. of a 3% amino acid mixture in glucose. Six of these febrile reactions occurred singly and the patients tested simultaneously experienced no abnormal reactions. Once a simultaneous reaction occurred in 2 individuals. The first experienced chills and fever up to 102° F. with extensive diaphoresis maximal 2 hours after the end of the infusion.

At other times no obvious reason for such febrile reactions could be found. In 2 patients suffering from tuberculosis a definite rise in temperature apparently directly related to the infusion was noted. A patient with pulmonary tuberculosis received a 3% solution in 5% glucose and saline over 45 minutes. He experienced a rise in temperature without chills reaching a peak of 102° F. within 2 hours after the end of the infusion. In 3 other cases of tuberculosis simultaneously tested with the same solution no reaction was observed. Another patient with tuberculosis of the spine and transverse myelitis experienced a temperature rise to 102° F. after an infusion of a 1.5% solution in 5% glucose. Five other patients experienced no symptoms with the same batch of amino acids. In this instance the febrile response could be repeated several days later when a 3% solution made from a different batch was offered within 30 minutes.

Another distinct type of reaction is characterized by flushing of the face, nausea and dizziness often associated with an explosive type of vomiting. In all but 1 of the 8 cases of this group the infusion was offered rapidly with an average infusion time of only 36 minutes as compared to 60 minutes infusion time seen with most of the other reactions (Table 2). into a definite pattern. In 4 cases severe headaches, precordial constriction and vague body pains, particularly noticeable in the lumbar region, were observed. In 1 of the patients, a sharp occipital headache occurred after the infusion bottle was accidentally shaken violently before the infusion was started. Two patients with severe anemia and atherosclerotic

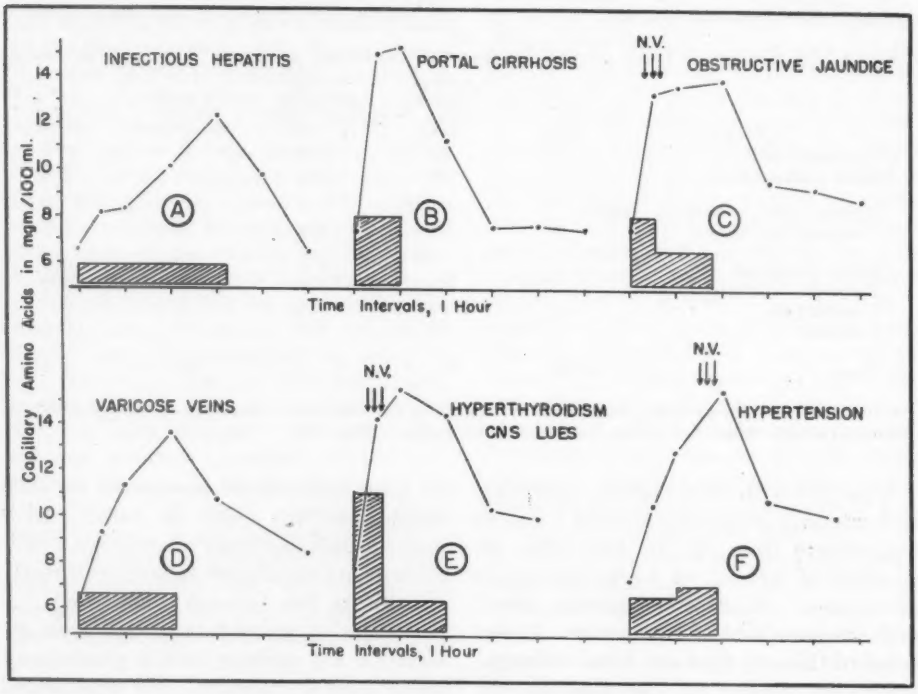

FIG. 1.—Emetic action of amino acids. *A*, *B*, *C*, cases of severe liver disease; *D*, *E*, *F*, no impairment of liver functions; *N*, *V*, nausea and vomiting. All patients received 45 gm. amino acids ("parenamine") intravenously. Nausea occurred in Cases *C*, *E* and *F* when the level rose above 13 mg./100 ml. It was observed at lower levels in others. The amino acid level in Patients *B* and *D* rose above 13 mg. without reaction. Note that there is no appreciable difference between cases with and without impaired liver function. The hatched squares indicate the amount of amino acids given per hour: *A*, 12.5 gm./hr.; *B*, 45 gm./hr.; *C*, 45 and 22 gm./hr.; *D*, 22 gm./hr.; *E*, 90 and 22 gm./hr.; *F*, 22 and 30 gm./hr.

The administration of amino acids proceeded almost twice as fast in this group as compared to others while the average concentration of the final solution did not differ from the rest. In some instances the symptoms disappeared when the speed of the infusion was reduced or a new infusion started at a slower rate (Fig. 1, *C*, *E*).

The other reactions noted do not fall heart disease experienced dyspnea at the end of the infusion, in 1 associated with an excessive sinus tachycardia.

Discussion and Further Observations. Of the amino acid infusions of this series, 1.5% were followed by a febrile response with or without chills. None was serious and all subsided within a few hours. Febrile reactions are relatively common in

occurrence whenever parenteral fluids are being administered. Recent reports on plasma, whole blood, or red cell transfusions show an incidence of approximately 2%.[7,11,35] A recent report on the reaction incidence of a red cell-glucose-amino acid infusion mixture lists 3.8% febrile reaction.[32] In some series, such reactions were encountered in as high as 10%[1] and 14%[8] of all transfusions given. Pyrexial reactions of this type are usually attributed to foreign protein and bacterial disintegration products which contaminate the fluid administered, tubing, glassware or needles used. In a series of 889 blood transfusions observed during 1930 and 1931 Lewissohn and Rosenthal reported a decline of febrile reactions when scrupulous technique in cleaning of instruments and tubing was instituted after the first 412 cases.[22] In the present series some of the reactions obviously could have been avoided but even so the incidence of febrile reactions (1.5%) does not appear higher than in comparable series of plasma or blood transfusions.

Febrile reactions are more likely to occur in severely anemic patients or in those suffering from infections of various kinds.[11,27] Some of the cases cited above seem to bear this out and a specific action of amino acids on the thermoregulatory centers cannot be excluded particularly when reactions of this type occur regularly and repeatedly in 1 case and not in others. Injections of crystallized amino acids in large amounts have resulted in febrile reactions in one series of cases.[33] That standing of a ready made-up infusion may result in febrile reactions has been reported[35] and was found once in the present series. A small number of bacteria in the infusion set-up may not interfere with the infusion, but further growth upon standing may be sufficient to elicit a febrile response. One should remember that an isotonic amino acid glucose mixture has been shown to be a perfect culture medium for bacterial growth.[4,21]

Overloading of the circulation by suddenly increasing the circulating fluid volume in the face of anemia and heart disease or both, is likewise known as an avoidable complication of transfusions in general.[37,39] A similar reaction was observed twice in the present study and could have been prevented by slowing of the infusion or by constant drip administration.

The importance of so-called nitritoid reactions following parenteral fluid administrations has recently been stressed by Strumia, McGraw and Blake.[35] Such reactions consisted in a sense of constriction of the chest, pain in the lumbar region, headaches and occasional nausea and vomiting. Four instances somewhat reminiscent of the syndrome were observed in the present series. In 1 instance nausea without vomiting occurred during the latter part and shortly after an infusion of 3% amino acids had been offered over a period of 130 minutes. The next day this patient reacted with a very severe headache when a 6% solution was offered within 125 minutes. No reactions were noted in a second patient who received the same solution simultaneously. It is felt that this patient might have undergone a nitritoid reaction. The nausea observed on the first trial was obviously not caused by rapid infusion responsible for a similar symptom in 7 other cases.

All these reactions are familiar wherever infusions of any type are given. Amino acid mixtures are not specifically responsible for them and they do not appear with greater frequency when amino acids instead of crystalloids or blood or plasma are being given by parenteral route.

On the other hand, hot flashes, nausea and vomiting which follow rapid administration of casein hydrolysates have been noted by several observers and they appear to be characteristic of reactions to such mixtures of amino acids. From Table 2 and from statements made by others, it appears obvious that these reactions have some relation to the speed with which the solution is being offered. This

is further suggested by the fact that these symptoms disappear soon after the end of the infusion or when the speed of inflow is reduced. A simple explanation suggests itself immediately: amino acids are resynthesized primarily in the liver and a discrepancy between the speed which such products are offered and the capacity of the liver to remove them from the blood stream might conceivably be a factor causing nausea and vomiting. This is quickly relieved by adjusting the speed of inflow to the rate of removal. If this assumption is correct, hyperamino-acidemia should be present in cases showing nausea but not in others or at least blood amino acid levels in these reactors should be considerable in excess of those found in persons not suffering from nausea and vomiting. Secondly, patients suffering from diseases of the liver with marked impairment of function would be expected to tolerate amino acids much less readily than normal individuals, would show a

TABLE 3.—AMINO ACID LEVELS OF CAPILLARY BLOOD AT INTERVALS FOLLOWING INFUSION OF 45 GM. AMINO ACIDS (PARENAMINE) (MG./100 ML)

No. cases	Reactions	Fasting	30 min.	1 hr.	2 hrs.	3 hrs.	4 hrs.	7 hrs.
7	None	7.3	11.0	11.6	12.7	10.4	9.2	8.5
5	Nausea, vomiting, hot flashes	7.3	10.5	12.6	13.1	11.2	9.4	8.7

TABLE 4.—AMINO ACID LEVELS OF CAPILLARY BLOOD FOLLOWING INFUSIONS OF 45 GM. AMINO ACIDS (PARENAMINE): CASES OF NORMAL AND ABNORMAL LIVER FUNCTION COMPARED (MG./100 ML.)

No. cases	Type and reaction	Fasting	30 min.	1 hr.	2 hrs.	3 hrs.	4 hrs.	7 hrs.
3	Normal,* no reaction	8.0	10.9	11.6	13.4	11.2	10.1	9.0
4	Normal, nausea, etc.	7.2	10.1	12.3	12.9	11.8	9.5	8.8
4	Abnormal,† no reaction	6.8	11.4	11.6	12.4	9.8	9.0	8.0
3	Abnormal, nausea, etc.	7.4	13.2	13.5	13.8	9.4	9.1	8.4
		6.9‡	10.3	10.3	10.3	8.1	6.5	6.5

* Normal: Dermatitis, varicose veins, paresis, hypertens on, bronchitis, bronchogenic carcinoma, mild toxic goiter.

† Abnormal: Portal cirrhosis of liver (5 cases), silent stone with obstructive jaundice, catarrhal jaundice.

‡ One patient with cirrhosis who received only 30 gm. amino acids (i.v.). Nausea and vomiting occurred during the 2nd hour of administration.

TABLE 5.—AMINO ACID LEVELS OF CAPILLARY BLOOD FOLLOWING RAPID INJECTION OF 7.5 GM. AMINO ACIDS (PARENAMINE)

No. cases	Type	Injection time, min.	Fasting	10 min.	30 min.	40 min.	50 min.	60 min.
1	Normal	10.0	8.8	..	7.8	7.5	7.5	7.9
2	Cirrhosis	10.0	8.2	..	8.7	9.5	9.4	8.4
3	Normal	5.0	7.8	12.4	10.7	9.3	9.1	7.9
5	Cirrhosis	5.0	7.5	12.3	10.2	8.6	9.1	9.1
1	Inf. hepatitis	5.0	8.1	12.5	10.4	8.5	9.5	7.4
1	Normal	2.5	7.8	14.8	11.3	9.6	8.1	8.4
2	Cirrhosis	2.5	8.5	12.8	11.3	9.9	9.0	8.9
1	Inf. hepatitis	2.5	7.9	10.9	10.0	7.8	..	7.9

No reactions occurred in any of the cases.

No rise of amino acid levels was observed when 7.5 gm. amino acids were offered within 10 minutes, apparently indicating that removal of amino acids from the blood stream occurred at a rate exceeding 0.75 per minute in the normal individual as well as in 2 cases of advanced portal cirrhosis (biopsy).

higher degree of amino-acidemia and might present a higher incidence of nausea and vomiting. Some evidence can be cited in support of this thesis. It has been stated that amino acids are not tolerated when icterus is present.[3,28] Reactions are said to be common in infectious hepatitis.[19] On the basis of the assumption mentioned above, cirrhosis of the liver has once been mentioned as a contraindication to parenteral amino acid administration.[3] Liver damage was said to be present in the fatal case reported by Curreri, Hibma and Cohen,[6] and was stressed as a complication by Hopps.[16] A decrease in plasma clearance of amino acids in hypoproteinemic dogs and in patients with diseases of the liver has been reported.[15,23] None of these statements, however, have gone unchallenged and in fact amino acid solutions have been used extensively in the treatment of cirrhosis of the liver[12,13,19] and in infectious hepatitis.[34]

In an attempt to obtain some information relative to the cause of this reaction amino acid levels were determined by measurements of capillary blood in a number of cases before, during and after parenteral infusion of amino acids. Of the 14 cases thus tested, 7 were patients suffering from a variety of diseases not severe enough to affect liver function appreciably, 5 had advanced portal cirrhosis confirmed by biopsy, 1 had severe obstructive jaundice of long standing (silent stone) and 1 had infectious hepatitis. All but 2 patients thus tested received 45 gm. of amino acids diluted to 1000 ml. of fluid with 10% glucose (4.5% solution). They were fasting and received no food for 7 hours after the beginning of the infusion. Table 3 reveals the absence of any significant differences in the amino acid levels in cases reacting with nausea and vomiting and in those tolerating the infusion. Furthermore, there appears to be no striking difference between cases with and without diseases of the liver, as indicated in Table 4. Although only a few cases were tested in this manner the results were consistent and the ranges of the amino acid concentration in the individual cases were not striking. However, from the inspection of some of the curves it appeared that the speed with which a higher amino acid level was obtained rather than the level itself may have been one factor responsible for the reactions (Fig. 1, *C*, *E*). A rapid rise was observed in other cases who did not suffer emesis (Fig. 1, *B*). It was found, for instance, that nausea and vomiting would occur when the level rose from 7.4 to 13.2 mg.% It subsided promptly when the speed of the infusion was reduced, although during the next 90 minutes the level rose from 13.2 to 13.5 and from 13.5 to 13.8 mg.% (Fig. 1, *C*). (The differences may lie within the error of measurement.) In another case nausea and explosive vomiting was present when the amino acid level ascended from 7.7 to 14.2 mg. within 30 minutes. When the inflow was adjusted the level rose still further to 15.5 mg. during the next hour but nausea subsided (Fig. 1, *E*). It was, therefore, surprising to observe that when amino acids were offered very rapidly with a syringe in 15 cases, not a single instance of nausea and vomiting occurred although steep rises in amino acid levels were present (Table 5). Again, in the small number of cases no significant differences were noted between cases with normal and abnormal liver function. Obviously, the speed of administration must be of some importance as repeated observations have shown that slowing of the infusion will prevent such reactions. Rapid administration of amino acids by syringe is necessarily limited as to the total amount offered and not more than 7.5 gm. parenamine was given in each case. The blood levels obtained, however, were comparable to those observed in patients receiving larger amounts over longer periods. In addition to the speed of administration one might assume that saturation of the liver with amino acids might be another factor concerned in the development of

nausea and vomiting. It appears, then, that the rapidity of the rise of amino acid concentration in the blood plus the total amount offered are the two important factors responsible for the reactions encountered.

It has recently been reported that certain amino acids, particularly glycine, glutamic acid and aspartic acid, may be responsible for intolerance.[24,25,26] In hypoproteinemic dogs no reactions occurred, in spite of extremely rapid administration of fairly large amounts when these substances were omitted from crystalline amino acid mixtures. In these series of experiments mixtures of crystallized amino acids were uniformly better tolerated than mixtures prepared from casein hydrolysates. This might be explained by the fact that in casein glutamic acid is present in amounts over twice as high as any other individual amino acid.[31] Our observations on total amino acid levels during and after infusions neither confirm nor deny these findings, but the fact that no correlation of the total amino acid level to intolerance was found would favor the concept that individual components of the mixture might be responsible for such reactions as hot flashes, nausea and vomiting. The amount of glutamic acid offered on rapid injection in the examples presented might not have been sufficient to reach a reaction threshold.

Another type of reaction which is regularly mentioned as typically associated with amino acid administration is the tendency of such mixtures to cause phlebothrombosis. This has been encountered frequently by us during the routine use of amino acid hydrolysates, although in the present study thrombosis was not encountered, because the time of infusion was short and the administration not repetitive. Both commercial preparations have a pH of about 4. When diluted to a 4% solution the mixture is equal in isotonicity to normal saline or 5% glucose. It has recently been stated that phlebitis is caused by the hypertonicity of the solution rather than by the amino acids themselves.[17] No more than 45 gm. of amino acids is usually given in 1000 ml. of a dilution fluid so that the assumption that phlebothrombosis is caused by the hypertonicity of the solution is rarely met under ordinary circumstances. It might again be possible that individual amino acids by themselves or by locally combining with other substances may be concerned in endothelial damage and intravascular clotting. Acidity of the final solution would hardly be a factor in the ordinary dilutions used.

Conclusions. The results of this study in general are in accord with the experiences of those who have used amino acids before. There is a definite but rather low incidence of reactions. Some are seen with any type of parenteral fluid administration, others are characteristic for solutions of amino acids. It appears justified to follow certain precautions when mixtures of amino acids of the types at present available are to be given parenterally:

1. In preparing the final solution utmost care should be taken to avoid accidental contamination in mixing or in starting the infusion. Glucose protein mixtures of the type used are perfect media for bacterial growth. The mixture should, therefore, be prepared by the physician who plans to use it and the procedure of dilution should not be left to the nursing staff. The recent introduction of a ready made solution of amino acids in glucose should go far to prevent febrile reaction caused by improper handling.

2. Once set up in the final dilution, the mixture should be given without delay.

3. The speed of flow should be adjusted so that not more than 15 gm. hydrolysate (100 ml. parenamine) are offered per hour (0.25 gm. per minute).

4. As endothelial damage and phlebothrombosis cannot be avoided when amino acids are to be given over a long period of time, a vein on the dorsum of the hand should be used and subsequent injections

should be given into the same vein, gradually moving the point of insertion proximally. Thus the vein can be used even if its distal end has become sclerosed and multiple thromboses of superficial veins can be kept to a minimum.

If these precautions would have been followed at all times during the present series, the incidence of reactions could have been lowered to at least 10 instead of 22 cases and uneventful infusion would have been observed in 98% instead of 93% of the cases. The incidence of pyrogenic reaction in this series was not greater than in any of the reported series of blood and plasma transfusions.

Summary. 1. Twenty-two reactions were observed in a series of 550 infusions of an amino acid solution (casein hydrolysate) given for the sole purpose of determining the incidence and character of reactions inherent to parenteral protein alimentation. The reaction incidence was 4%.

2. Eight of these reactions consisted of sudden onset of fever with and without chills (1.5% of all infusions). It does not seem justified to attribute the pyrogenic reactions to the acid hydrolysate administered. In a number of cases accidental contamination appeared likely, in others tubing reactions might have been responsible. In still others, a rise in temperature was noted without an apparent exciting cause.

3. Nausea with or without vomiting may occur when the speed of administration exceeds 15 gm. per hour. Blood amino acid levels taken during this period showed little difference when those reacting with nausea and those tolerating the infusion were compared. It is likely that the steepness of ascent of amino acid levels plus the total amount of amino acids offered were responsible for the reactions of this type. These findings favor the view that some individual components of the mixture may be responsible for nausea and vomiting produced by solutions of this type.

4. Under conditions of these experiments, cases with diseases of the liver did not appear to react differently as compared with others.

5. Certain recommendations are made which, if followed, should reduce reactions to parenteral amino acid administration to the unavoidable minimum.

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MALARIAL JAUNDICE

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Jaundice is known to occur in malaria,[8] as indeed is hardly surprising in a hemolytic disease, but it is uncommon. The clinical records of the 20th General Hospital, a United States Army installation located in Assam Province in India, make available for study 8837 cases of malaria occurring between May 1, 1943, and Sept. 1, 1945; and it has been thought worth while to review this material to the end of elucidating the clinical syndrome of malarial jaundice.

Method of Study. The records of the clinical laboratory were scrutinized and all reports (321) submitted by the laboratory of a quantitative van den Bergh exceeding 0.6 mg. % or an icterus index exceeding 10 were collected.* The clinical records of all these patients were then inspected and all those which showed the occurrence of malaria at or near the time the patients were jaundiced were put aside for study. These charts numbered 30 and comprised the available case records of all our patients who had jaundice in close association with malaria during the period covered by this study.

It soon became apparent that 24 of the 30 patients exhibited a unified clinical syndrome which unquestionably represented malarial jaundice. Briefly this was characterized by the sudden onset of painless hemolytic jaundice of varying degree during an attack of malaria, in all instances while the patient was still febrile, which subsided rapidly and completely, and which was perfectly benign provided it was uncomplicated.

Six of the 30 records were excluded from the study. Two were those of patients treated elsewhere for malaria and transferred here afebrile and asymptomatic, each of whom had a slight elevation of serum bilirubin on admission (van den Bergh 0.9 mg. and 0.8 mg. per 100 cc., respectively). These patients may have had malarial jaundice, but we have insufficient data to draw any conclusions. Another patient developed falciparum malaria on the 11th day of a perfectly typical catarrhal jaundice. The other 3 patients became jaundiced either during a malarial attack or (2 cases) 1 to 3 days thereafter; but the long duration of the jaundice, and the onset of the disease, with constipation and dull abdominal distress, clearly demarcated it from the syndrome of malarial jaundice; and in addition their jaundice was not of the hemolytic type, as none was anemic and the 2 who had more than one hemoglobin estimation showed no fall during their disease.

Analysis of Cases. Table 1 records the clinical and laboratory data in the 24 cases of malarial jaundice studied. The admission histories (with the exception of Case 8, in whom no adequate history was obtainable) recounted in general the banal symptoms of an acute attack of malaria. Unusual features in any patient's record are noted in Table 1 and in the appended comment.

Comment. 1. *Age, Race and Incidence.* Malarial jaundice appeared in 0.27% of our patients with malaria (24 of 8837). All were soldiers of the Chinese or American Army, and only 7 were older than the 3rd decade. Table 2 shows percentage calculations based upon nationality and parasite species. Malarial jaundice was about 4 times more common in falciparum than in vivax malaria; but nationality did not appear to influence its incidence. Jaundice was not seen in 100 cases of quartan malaria.

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TABLE 1.—ANALYSES OF DATA OF 24 CASES OF MALARIAL JAUNDICE

Case No.	Age, Race	Prior med.	Abdominal	M.P. smear	van den Bergh	Icterus index	Jaundice	Duration	Hemoglobin	Urine	Liver	Spleen	Complication	Treatment	Comment
1	22 Ch	?	0	F +++	.....	26 (8th) 6 (12th)	+ (5th) 0 (11th)	6	12.5 (5th) 10.5 (8th)	B: 0 (8th)	+ T	+	? C	Q A	
2	25 Ch	?	0	F +++	.....	43 (5th) 7 (11th)	+ (4th) ++ (6th) + (8th) 0 (11th)	7	14.0 (4th) 13.2 (5th)	Dark (4th) B: 0 (5th)	0	0	0	Q A	
3	19 Ch	Q A	0	F ++	.....	28 (5th) 7 (9th)	.....	4	14.2 (4th) 11.2 (9th)	.....	0	0	0	Q A	
4	21 Ch	0	0	F +++	.....	14 (8th)	+ (5th) ++ (8th) 0 (11th)	6	10.2 (5th) 9.2 (7th) 7.5 (10th) 9.2 (24th)	.....	0	+	? C	A	Stool + B (8th)
5	29 Ch	0	0	V +++	.....	17 (9th)	0 (8th) + (9th) 0 (17th)	8	15.0 (5th) 11.5 (9th) 11.0 (14th)	.....	+ T	+	0	Q A	Stool +B (8th and 12th)
6	47 W	Q A	0	F	1.6 (9th)	18 (9th)	+ (7th)	?	12.3 (8th) 10.8 (12th)	.....	+ T	0	0	A	
7	30 Ch	?	?	F +++	.....	35 (7th)	+ (6th)	(2)	8.4 (7th)	B: + (6th) B: + (7th) Ur: + (7th)	0	+	C	Q A	Died
8	27 W	?	0	F +++	5.0 2nd Hosp. Day	.....	+ 1st HD ++ 2nd HD	(4+)	.....	Orange: (1st) B: + (2nd) Hb: 0 (3rd)	+	0	C	Q A	Died
9	20 Ch	Q A	0	F +++	.....	21 (7th) 20 (8th)	+ (7th) + (10th) 0 (12th)	5	17.0 (3rd)	Dark (8th) B: 0 (9th) Ur: (9th)	++	+	0	Q A	
10	28 Ch	Q A	0	F +++	1.8 (6th)	22 (6th)	+ (5th) 0 (by 17th)	12	7.1 (5th) 7.2 (6th) 9.0 (17th)	.....	0	+	? C	Q A	
11	31 Ch	Q A	0	V +	.....	13 (5th)	+ (3rd)	?	....	...	0	+	0	Q A	
12	31 Ch	A	0	F +++	.....	26 (7th)	+ (7th) 0 (by 16th)	9	.....	B: + (8th)	++	+	0	Q A	
								?	.....	.....	0	+	0	A	

11	31 Ch	Q A	0	V +	.....	13 (5th)	+ (3rd)	?	....	...	0	+	0	Q A	
12	31 Ch	A	0	F +++	.....	26 (7th)	+ (7th) 0 (by 16th)	9	.....	B: + (8th)	++	+	0	Q A	
13	22 Ch	0	0	F ++	2.4 (3rd)	.....	.....	?	.....	.....	0	+	0	A	
14	20 Ch	0	0	F ++	3.0 (4th) 0.9 (6th)	.....	+ (4th) 0 (6th)	2	15.0 (5th)	.....	0	+	? C	SN 6911	
15	20 Ch	0	0	V ++	1.0 (4th)	.....	+ (3rd)	?	16.0 (3rd)	.....	0	0	0	A	
16	24 Ch	0	0	F +	2.0 (9th)	16 (9th)	+ (5th) 0 (by 12th)	7	13.5 (8th) 18.0 (13th)	.....	0	0	0	Q A	
17	22 W	Q A	0	Pos. Und.	8.5 (5th) 1.0 (13th) 0.7 (20th)	61 (5th) 12 (13th) 10 (24th)	+ (4th) + (8th) 0 (13th)	15	16.0 (5th)	B: + (5th) Ur: + (5th) Hb: + (5th) RBC: 0 (5th)	0	0	? C	Q A	
18	21 W	0	0	V ++	1.4 (3rd) 0.4 (7th)	.....	+ (2nd)	5	14.0 (3rd)	.....	0	0	0	A	
19	22 W	0	0	V ++	1.8 (2nd)	.....	+ (1st) 0 (by 9th)	8	11.0 (2nd) 12.0 (8th)	B: 0 (2nd) Ur: 0 (7th)	0	0	0	A	
20	34 W	0?	0	F +++	.....	55 (4th) 9 (25th)	+ (4th)	?	11.0 (4th)	B: + (4th) Hb: + (4th)	+	0	Az	Q A	BUN 105 (4th)
21	20 W	Q A	0	F +++	2.4 (6th)	21 (6th)	++ (5th) ± (11th)	?	4.6 (3rd) 7.3 (6th) 15.0 (34th)	.....	+	+	0	Q A	
22	33 N	0	+	F ++	.....	12 (7th)	+ (2nd)	?	.....	B: + (4th) B: + (6th)	0	0	0	Q A	Diarrhea
23	24 Ch	A	+	F +++	.....	12 (7th)	+ (6th)	?	15.0 (4th)	B: + (6th)	++	++	0	A	Diarrhea
24	21 W	0	+	F +++	9.0 (2nd)	.....	+ (2nd) ++ (3rd) +++ (4th)	(3)	8.5 (2nd)	B: + (1st) Ur.: (1st) Hb: 0 (1st) B: + (2nd) Hb: + (2nd)	+ T	+	C Az	Q A	Died BUN 113 (2nd)

NOTE.—Q: Quinine. A: Atabrine. B: Bile pigments. Ur: Urobilin. Hb: Hemoglobin. T: Tender. C: Cerebral malaria. Az: Azotemia. Numbers in parenthesis refer to day of disease (except in Case 8).

2. *Abdominal Symptoms.* Though nausea and vomiting were not uncommon, abdominal distress of any type occurred in only 3 patients, all of whom had falciparum malaria. Two of them (Cases 22 and 23) complained of cramping pains, quite unlike the dull distress of catarrhal jaundice; and both these soldiers were passing, at the time, frequent watery scanty stools which contained no blood or pus. This syndrome was not rare in our malarial patients and was thought to be a mild malarial dysentery. The third patient (Case 24) had fairly severe steady right upper quadrant pain unassociated with diarrhea.

3. *Smear for Malaria Parasites.* Five patients had trophozoites of *P. vivax* in the blood smear; 18 showed trophozoites of *P. falciparum.* No mixed infections occurred. One patient (Case 17) showed a plasmodium the species of which was undetermined; his disease has been considered to be falciparum malaria because of the clinical phenomena of severe dizziness, so common in falciparum malaria, and sustained high fever. Two seriously ill patients (Cases 8 and 24) showed also quantities of segmenting forms of *P. falciparum* in the peripheral blood. One patient (Case 19) showed numerous merozoites of *P. vivax.*

As was to be expected, *P. falciparum* gave rise in general to a more severe illness than did *P. vivax.* All 3 fatalities were due to *P. falciparum* infections, as were the more severe grades of jaundice. *P. malariæ* was demonstrated in none of these patients.

4. *Jaundice.* The calculation of the mean duration of jaundice is subject to several inaccuracies. The day of appearance of icterus in 11 instances was subsequent to the day of admission, and consequently was fairly accurately determined. In the 13 patients in whom jaundice was present on admission, the day of onset was taken to be the day of admission, thereby probably introducing a slight error. On the other hand, the date of the disappearance of clinical jaundice was not always evident from the record. A normal or practically normal laboratory determination of serum bilirubin was utilized in fixing the limit of jaundice where one could be sure that the jaundice had not disappeared more than a day or 2 prior to the normal reading. In 8 patients, information on this point was insufficiently accurate, and no calculation has been made of the duration of their jaundice. The 3 patients who died while still jaundiced also did not figure in the estimations of the duration of icterus.

TABLE 2.—RATIO OF MALARIAL JAUNDICE TO TOTAL MALARIA BY GROUPS

	Chinese	American	Total
Vivax	$\frac{2}{1361} = 0.14\%$	$\frac{3}{2605} = 0.11\%$	$\frac{5}{3966} = 0.12\%$
Falciparum	$\frac{13}{3300} = 0.4\%$	$\frac{6}{1471} = 0.4\%$	$\frac{19}{4771} = 0.4\%$

The average duration of jaundice as calculated in the remaining patients was 7 days, with a maximum of 15 (Case 17) and a minimum of 2 (Case 14). The average day of onset was the 4th day of fever, and varied between the 1st and the 7th.

The fact that our patients had serum bilirubin determinations by 2 different techniques introduced a problem in the evaluation of the average maximal bilirubinemia, since it is not possible[7] to assume an accurate equivalent icterus index for a given van den Bergh reading, or *vice versa.* However, by counting only one of the laboratory methods in each of the 5 patients who had serum bilirubin estimations by both techniques—the icterus index in Cases 17 and 21 and the van den Bergh in Cases 6, 10 and 16—an average maximal van den Bergh of 2.4 mg. per 100 cc. was obtained in 10 patients, and an average maximal icteric index of 27 in the other 14 pa-

tients. Since these figures are roughly equivalent, it is felt that the calculation is substantially as accurate as it would have been had only one method been used. There remains, of course, the error introduced by the unlikelihood that blood samples were taken at the height of the jaundice in all cases.

The qualitative van den Bergh reactions have not been tabulated. All the sera which gave a very high quantitative titer showed a strong direct reaction. No immediate reaction was obtained when there was only slight quantitative elevation. The intermediate quantitative readings were accompanied by biphasic qualitative reactions.

5. *Hemoglobin.* In only 6 of our patients were hemoglobin determinations made which spanned the period during which the icterus was waxing (Cases 1 to 6). In all 6 there was a fall in hemoglobin compatible with rapid destruction of red blood cells. The mean fall measured 2.25 gm. % measured over a mean time interval of 3.7 days. The determinations were not systematic enough to yield information concerning the relative quantity of erythrocyte lysis in any given patient; what they do show is that in all 6 cases definite blood destruction accompanied the rising serum bilirubin; and one may safely conclude that their jaundice was of the hemolytic variety.

There is every reason to suppose that the other patients' jaundice was on the same basis. Many of them were admitted already jaundiced and, as would be expected, their admission blood counts almost always showed a rather marked anemia. An occasional patient (Cases 9 and 23) had a single reading 3 to 4 days before jaundice appeared, and they showed no anemia. Only 1 patient (Case 17) had a single normal reading at a time when he was becoming jaundiced.

It is concluded that malarial jaundice is of the hemolytic variety.

6. *Urine.* (*a*) Bile pigments: The urine of 11 of these patients was not tested for the presence of bile pigments. Of the remaining 13 patients, 9 passed urine containing bile by chemical test. The laboratory returned a negative report on the urines of the 4 remaining patients. However, 2 of these men had passed a dark colored urine the day before the specimen examined by the laboratory was collected. Apparently bilirubinuria is the rule in this syndrome.

(*b*) Hemoglobinuria: Three patients passed free hemoglobin in their urine. In 2 of them (Cases 20 and 24) the characteristic reddish color was present and the benzidine test was positive; in the 3rd (Case 17) no mention is made of the color, but the benzidine test was positive on a urine which contained no red blood cells. A 4th patient (Case 8) probably had hemoglobinuria; his urine was described as "brownish orange," but no benzidine test was done until the 2nd day, at which time the urine was no longer reddish but dark brown, and was benzidine-negative, though positive for bile. This patient is the only one of whom it is specifically stated that no antimalarial drug had been taken prior to the appearance of reddish urine.

The prime importance of the fact that *these 4 patients had the highest elevations of serum bilirubin* in our whole series will be further discussed.

7. *Stools.* Stool pigment has not been tabulated because it is mentioned specifically in only 2 patients, both of whose feces contained bile. It is quite unlikely that acholic stools passed by febrile jaundiced bed patients would escape the attention of the ward officer. Presumably most of the stools contained excess bile.

8. *Liver and Spleen.* The liver was enlarged in 10 of our cases, in 3 of which it was tender. The spleen was palpable in 13.

9. *Complications.* (*a*) Cerebral malaria: A number of patients, without exhibiting full-blown cerebral malaria, gave evidence of mild central nervous system irritation. Those who, in addition to severe headache, had any of the phenomena of severe dizziness, stiff neck, mental dullness, or reflex

changes are tabulated as questionable cerebral malaria.

Three patients (Cases 7, 8 and 24) had undoubted cerebral malaria; and in all the disease ended fatally. All were stuporous to unconscious throughout their hospital course (3 to 4 days); and all had reflex abnormalities and positive Babinski signs. Two (Cases 8 and 24) expired in deep coma, the other after 2 severe generalized convulsions.

Cerebral involvement appears to bear no relation to icterus in malaria. The 3 cases of cerebral malaria represent a small fraction of the total number of patients with that disease seen here during the period covered by this study, and of course none of the others was jaundiced.

(*b*) Azotemia: Two patients developed a severe acute azotemia as manifested by B.U.N. determinations of 105 and 113, respectively. One of them (Case 20) entered the hospital deeply jaundiced and in stupor, but he was vigorously treated with quinine and atabrine and his fever subsided. He had transient hypertension. Although his icteric index and B.U.N. were normal after 3 weeks, he was still unable to concentrate his urine above 1.012.

The other patient (Case 24) was one of the 3 cases of cerebral malaria. He was admitted in stupor, sank slowly into deeper coma, and expired quietly on the 3rd hospital day. It seems probable that the cause of death was cerebral, although nitrogen retention, measured on the 2nd day, was marked.

It is of interest that these 2 azotemic patients constitute 2 of the 3 patients who had definite hemoglobinuria. That the association is more than coincidental is further suggested by the fact that the patient (Case 8) who passed brownish orange urine which was not submitted to chemical examination had a B.U.N. of 34; and that no other patient in our series was reported to have a B.U.N. above 22. The subject will be further discussed in a later section of this paper.

10. *Medication.* Because of the possible relationship of malarial jaundice to blackwater fever, in which condition quinine has been thought by some to play a pathogenetic rôle, and because it is known that atabrine may under some circumstances be hepatotoxic,[4] both the ingestion of these drugs shortly prior to the appearance of jaundice and their therapeutic exhibition in this hospital have been tabulated. Ten patients had taken neither drug therapeutically prior to the onset of icterus, and only 1 of this group (Case 24) had been receiving suppressive therapy with atabrine. Nine had been treated with atabrine and 7 with quinine. There is therefore no indication that either drug played any part in the production of jaundice.

No patient was treated here with quinine alone. Seven received atabrine alone, and the average duration of their jaundice was 7 days—precisely the same as in those patients who also received quinine. Evidence is lacking to convict either drug of prolonging the jaundice.

It is noteworthy, but probably of no significance, that the shortest-lived jaundice occurred in the 1 patient who was treated with a new antimalarial chemical, SN-6911 (Case 14).

11. *Autopsy Material.* Three patients died (Cases 7, 8 and 24) and postmortem examinations were performed on all. All showed congestion and edema of the brain, liver, kidneys and pancreas. Pigment macrophages crowded the capillaries of all the organs. The livers were grossly firm and congested; the sinusoids were wide; the cords pale, granular and swollen, and contained large amounts of pigment granules (hemosiderin). The microscopic appearance of liver tissue was thought to indicate the presence of hepatic damage.

Discussion. 1. *Hemolysis and Liver Damage.* It is a familiar fact that in hemolytic icterus of any type some impairment of liver function occurs which acts as an accessory in the production of jaundice. Rich[6] has pointed out that 95% of a dog's liver can be excised with-

out producing jaundice, and has suggested that anoxemia of the hepatic cells resulting from anemia may account for failure of liver function in hemolytic diseases. The microscopic sections of liver tissue in these cases make one speculate whether the flooding of the organ with pigment, not only in the endothelial and Kupffer cells, but in the parenchyma as well, may not have some toxic effect. Using the bromsulfalein excretion test, Machella, Burgoon and Fine,[3] working at this hospital, have presented evidence that fever itself may depress hepatic function. They found that in 36 attacks of *P. falciparum* malaria in Chinese soldiers there was abnormal dye retention during the febrile period; and they were able to demonstrate retention of the same order of magnitude in 3 febrile subjects in whom pyrexia was induced artificially by the injection of typhoid vaccine.

Whatever the cause, it is clear that the liver is damaged in malarial jaundice. The sections afford evidence of degenerative changes in the parenchymal cells, and the presence of a direct van den Bergh reaction and of bile in the urine in many instances is indicative of intrahepatic microscopic regurgitation into the blood stream of cholebilirubin.

Serial dye excretion studies in 3 of our mildly jaundiced patients[3] show that the hepatic dysfunction is transient, at least in the milder grades of jaundice. Abnormal dye retention 1 week after the temperature returned to normal was minimal.

2. *Hemoglobinuria and Blackwater Fever.* The presence of hemoglobinuria in 3 and probably 4 of our cases calls for further discussion.

In every malarial chill there is, of course, more or less destruction of red blood cells; indeed, fever is not believed to be produced unless at least 1 in 10,000 red cells are parasitized.[12] The cases presented in this paper are those in which the amount of pigment so liberated into the blood stream has been sufficient to exceed the reserve capacity of the liver to excrete it as bile, with resulting bilirubinemia and jaundice.

Dameshek and Schwartz[1] have shown that hemoglobinuria will occur when a hemolytic reaction attains sufficient intensity. In their experiments they prepared in rabbits a hemolysin against guinea-pig red cells. When a small amount of this substance was injected into guinea-pigs, a subacute hemolytic anemia ensued; a larger amount resulted in acute hemolytic anemia, and a still larger quantity produced acute fulminating anemia with hemoglobinuria.

That their findings apply equally to malarial hemolysis is attested by the fact that of the 4 patients in our series who had the most intense hemolysis as gauged by the height of the serum bilirubin, 3 showed hemoglobinuria and the 4th probably had it; and none of the others did.

The renal threshold for hemoglobin is rather high; Tonfick[11] observed that the plasma must be quite pink before hemoglobinuria can occur, and Pierce[5] has calculated that in man the blood must contain at any given time 0.06 gm. of free hemoglobin per kilo of body weight before that substance can appear in the urine. In a 70 kilo man with a plasma volume of 3.8 liters, this would represent a plasma level of approximately 110 mg. per 100 cc.

It is unfortunate that we have no studies of plasma hemoglobin in any of our cases; but it is reasonable to assume that those patients who showed evidence of acute hemolysis only slightly less severe than our 3 patients with hemoglobinuria would have shown definite hemoglobinemia. The studies of Voigt and Voigt[13] indicate that hemoglobinemia is by no means rare in uncomplicated falciparum malaria. They determined the plasma hemoglobin in 17 patients during an attack of that disease, and found that 9 showed none, 4 traces, and 4 levels varying from 22 to 60 mg. per 100 cc.; 25 normal control subjects never exceeded a level of 19 mg. per 100 cc. In 4 of 17 cases of ordinary falciparum malaria, then, significant hemoglobinemia was pres-

ent—a figure which suggests that the condition is vastly more common in falciparum malaria than is clinical jaundice, and therefore that less hemolysis is required to produce definite elevation of serum hemoglobin than to cause jaundice.

Hemoglobinemia reflects the functional failure of the reticulo-endothelial system to keep the plasma clear of hemoglobin by converting it promptly to hemobilirubin. Hemoglobinuria represents a far more advanced degree of functional impairment, inasmuch as the plasma hemoglobin cannot be kept below the renal threshold. The latter condition is far less common; it is also far more serious, for it at once jeopardizes renal function, whereas hemoglobinemia *per se* appears to entail no particular deleterious consequences.

The continuity of our cases, ranging as they do from minimal hyperbilirubinemia to marked icterus with hemoglobinuria, conveys no hint that metabolic idiosyncrasy is playing any rôle; and the conclusion is drawn that *hemoglobinuria will appear in malarial jaundice when the usual hemolytic mechanism present in the disease becomes so intense and acute that the reticulo-endothelial system is unable to keep the plasma hemoglobin level below the renal threshold.*

None of our cases merits the appellation of blackwater fever; yet, although we have not seen that condition, it is believed that some light may be shed upon its etiology by a consideration of the cases here reviewed. According to Stitt,[9] its pathognomonic features are explosive, severe hemolytic anemia and jaundice with massive hemoglobinuria accompanying an unusually prostrating chill in a patient with malaria. It is easy to understand how clinicians, observing the striking picture of prostration, the massive hemoglobinuria, and the greatly enhanced mortality of the condition, should suppose that they were dealing with some etiologic factor in addition to that of an egregiously severe malarial hemolysis.

From what has already been said, however, it is clear that hemoglobinuria may be expected in severe malarial jaundice. Fairley and Bromfield[2] found that the average maximal indirect van den Bergh reaction on the sera of 20 patients with severe blackwater fever was 10.7 mg. per 100 cc.—a figure approaching 5 times the average maximal of our cases, though but slightly higher than the 2 highest readings of our series (9 mg. and 8.5 mg.), both of which occurred in patients in whom hemoglobinuria was present. As regards the high mortality rate of blackwater fever, Stitt states[10] that "the prognosis is especially dependent upon the amount of red corpuscles destroyed and whether the kidneys continue to function." Peculiarly significant, therefore, is the fact that the 2 of our patients (Cases 20 and 24) who had the most severe hemolytic reaction, and whose urines were among the 3 which definitely contained hemoglobin, developed a severe acute nitrogen retention (B.U.N. 105 and 113, respectively), and, in the case of the former, evidence of serious derangement of renal function (impaired urinary concentration).

It is suggested that our cases exhibit a series of instances of malarial hemolysis ranging from the least amount required to produce icterus to a severe jaundice with hemoglobinuria which is just short of true blackwater fever; that a somewhat more hyperacute malarial hemolysis than we have seen would exemplify the blackwater fever syndrome; and that the appearance of hemoglobinuria, with its threat to renal function in an acutely ill febrile patient, though implying an abrupt enhancement of the risk to health and life, does not necessarily indicate any etiologic hiatus nor imply any causative factor other than unusually severe malarial hemolysis.

Summary and Conclusions. Analysis is made of 24 cases of jaundice caused by malaria, comprising 0.24% of 8831 cases of malaria treated in the 20th General Hospital over a 28 month period.

Malarial jaundice is a distinct clinical entity characterized by the abrupt onset

of painless icterus in a febrile patient suffering with malaria. It is of short duration, averaging 7 days in our series. Enlargement of the liver and bilirubinuria are common; acholic stools probably do not occur. It is 4 times more common in falciparum than in vivax malaria.

It is primarily a hemolytic icterus, but hepatic injury secondary to hemolysis and fever contributes to the production of jaundice. There is no evidence that quinine or atabrine have any part in its pathogenesis.

Hemoglobinuria is the rule in exceptionally severe malarial jaundice. Because of its threat to renal function it is a complication to be dreaded. The mechanism of its production is discussed. Cerebral malaria probably accounted for all 3 fatalities in our series, but its incidence appears to be unrelated to the presence of jaundice. Uncomplicated malarial jaundice is benign.

The relationship of malarial jaundice to blackwater fever is discussed.

ADDENDUM. Since the completion of this paper, Major T. E. Machella has informed me that in the earliest days of this hospital he cared for 3 patients with unquestionable blackwater fever. It is a great misfortune that their records are no longer available, as they would have completed the continuity of a series of patients with malarial jaundice seen in this hospital ranging from minimal icterus up to and including the blackwater fever syndrome.

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PURPURA AS A COMPLICATION OF MALARIA

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A complication of a disease, although it may occur only once in 1000 cases, becomes important when millions of men are exposed to this disease, especially if the complication is a serious one and the danger to life is great. This is true of hemorrhage or purpura which occurs during the course of malaria, or as a result of drug therapy in malaria.

Purpura as a complication of malaria has been noted in the past by various investigators, although reports on this subject have been infrequent during the past 2 decades. Paisseau and Lemaire[10] observed hemorrhagic manifestations between the 1st week and the 2nd month after primary infection with plasmodia. "They have met with cases of simple purpura, manifested in fine petechiæ all over the body but particularly abundant on the legs, and characterized by a complete absence of pyrexia; of simple purpura shown in extensive ecchymoses and associated with ordinary 'pernicious' symptoms; of hemorrhagic or hemophilic purpura, where the cutaneous ecchymoses are quite overshadowed by hemorrhages from the mucosæ and particularly epistaxis, and the peripheral blood contains many immature elements and basophil multinuclears; of hemoglobinuric purpura, in which, besides petechiæ and ecchymoses and epistaxis and bleeding from the gums, hemoglobinuria was a conspicuous symptom only 4 days after the initial paroxysm of a primary infection; and of pernicious subicteric anemia, where within 23 days of the initial (and probably primary) infection, extremely severe epistaxis, concurrent with ecchymoses and petechiæ, were prominent symptoms of a progressive anemia that ended fatally within a month."

Christin[3] reported a case of purpura involving both skin and mucous membranes occurring in a chronic malarious subject who had marked anemia and leukopenia. Lorando, Chaniotis and Choreftis[5] recorded a case of tertian malaria in which each febrile attack was followed by an urticarial eruption accompanied by the appearance of purpuric patches. Mickaniewski and Hai[8] described 5 cases of purpura in Indo-China occurring in 3 young men, a woman, and a girl of 15, all of whom were suffering from chronic subtertian malaria of several years standing. None of them had taken quinine.

Purpura occurring as a result of the use of antimalarial agents, particularly quinine, has also been recorded. Thus, Deeks[4] referred to hemorrhages into the mucous membranes and extensive purpura as a complication of malaria treated with quinine. Vialatte and Remontet[17] reported a case of purpura due to quinine used as a suppressive antimalarial agent. Regendanz[12] noted the occurrence of petechiæ when quinine was used for malaria prophylaxis in troops. Barnes[1] observed purpura in a Chinaman treated with quinine. Maritschek and Markowicz[7] reported a case of recurring purpura due to quinine. Manson-Bahr,[6] Quick,[11] Christian,[2] Sollmann,[13] and Solis-Cohen,[14] among other authorities, have commented upon the fact that quinine therapy may result in purpuric manifestations. Nocht and Mayer[9] stated: "It is not yet known for certain to what extent hypersensitivity to quinine and in particular the hemorrhagic diathesis frequently occurring after quinine is due to concurrent malaria infection. But it seems as if in some cases the tendency to hemorrhage after the administration of quinine can be induced by malaria alone without a previous misuse of quinine

being in any way responsible. On the other hand, severe, even fatal, hemorrhages after quinine have been observed for which malaria was in no way responsible."

Data. The records of 10,000 consecutive cases of malaria in Gorgas Hospital were checked for hemorrhagic complications. Of these 10,000 patients, 6000 were treated with quinine, 2500 with atabrine. Ten patients (0.1% of the total) showed evidence of purpura. In only 1 instance (Case A) (0.01% of 10,000 cases) was purpura present before treatment. In the other 9 cases purpura occurred after treatment with quinine. The incidence of purpura in individuals treated with quinine, used alone or with atabrine, was 9 in 7590 (0.12%). There was not a single instance of purpura in a patient given atabrine alone.

In 9 cases the purpura occurred from 1 to 8 days following the onset of clinical symptoms of malaria. In each instance, however, the purpura followed the institution of quinine therapy. Six of these patients had been treated for malaria with quinine prior to the current infection or had been on "suppressive" or "prophylactic" quinine therapy. Of these, 1 (Case J), who had previously been on suppressive quinine therapy without symptoms, developed subconjunctival hemorrhages when treated with quinine for his first attack of malaria in March 1942. In April 1942, he had his second attack of malaria, which was treated with atabrine without the development of hemorrhagic manifestations. At the onset of the last attack of malaria, on May 20, 1942, the patient took 0.67 gm. of quinine and noted ringing in his ears and dizziness. On admission to the hospital, May 24, 1942, bilateral conjunctival hemorrhages were noted. The other 5 patients had no history of previous purpuric manifestations.

With but 1 exception, all of the patients were young, adult, white males who were members of the U. S. Army. The 1 exception was a middle-aged, white American male (Case 1). In no instance was any history of an allergic background elicited on the part of a patient or a patient's family.

The clinical and laboratory data of the 9 patients (Cases B and J) who developed purpura after receiving quinine are summarized in Table 1. The determination of the severity of the illness was based upon the clinical course of the primary illness, namely malaria, and the severity and extent of the purpura. In 1 patient (Case E) there was the complication of oliguria. Terminal pulmonary edema was present in both patients who died.

The treatment of the 9 patients was essentially similar. In all, quinine was discontinued and atabrine substituted. Six received infusions of saline and glucose; 3, whole blood transfusions; and 1, blood plasma. Oxygen was administered to 3 and "alkalinization" was attempted in 3. Antihemorrhagic agents such as calcium gluconate and vitamin K were employed in the treatment of 2 patients.

Illustrative Case Reports. CASE A. A 33 year old, white soldier was admitted complaining of dull headache, weakness, generalized body aches, bloody vomitus, and diarrhea of 4 days' duration. The temperature was 104.2° F., pulse was rapid, weak, and thready (rate about 200 per minute), blood pressure was 95 mm. of mercury systolic and 65 mm. of mercury diastolic. Subconjunctival hemorrhage, icteric tinge to scleras, herpes labialis, small hemorrhagic areas scattered throughout the buccal mucous membrane and soft palate, pharyngitis, palpable tender spleen, and a palpable tender liver were noted on physical examination. The bleeding time was 3 minutes; the coagulation time, 3½ minutes. *Plasmodium falciparum* was found in the blood film. The patient was placed upon quinine therapy despite the presence of purpura and was given supportive treatment. In all, he received 34 gm. of quinine in a 16 day period, and his response to the therapy was excellent. He improved markedly within 24 hours and all evidences of malaria and of the purpura disappeared within 5 days of the beginning of therapy. This, then, is an example of purpura occurring apparently as a part of the malarial picture before any antimalarial drug was given and responding excellently to quinine therapy.

CASE F. A 31 year old, white Army officer was admitted complaining of chills, fever, general malaise, slight cough, weakness, and headache of 2 days' duration. The patient had a temperature of 104.4° F., hot, dry skin, conjunctivitis, injected pharynx, tachycardia, and a palpable spleen. The

TABLE 1.—DATA ON 9 CASES

Case	Type of malaria	History taking quinine previously	Total quinine taken before onset of purpura (gm.)	Time between first dose and onset of purpura (hrs.)	Purpuric manifestations	Platelet count (thous. per c.mm.)	At time of purpura: Bleed. time (min.)	At time of purpura: Coag. time (min.)	At time of purpura: R.B.C. count (mill.)	Duration of purpura (days)	Severity of illness
B	*P. vivax*	+	5.0	29	Subconjunctival hemorrhage	102	Not done		3.93	1	Mild
C	*P. vivax*	+	2.67	Less than 12	Petechiæ over anterior aspects of both legs, upper extremities and thorax	24	2½	4½	3.75	3	Mod.
D	*P. vivax*	+	2.67	Noted in 1st urine spec. follow. drug	Erythrocytes in urine; bloody sputum	36	2½	4	3.65	1	Died
E	*P. falciparum*	+	2.0	16½	Bloody vomitus; tarry stools; blood in urine; bloody sputum	49	Not done		2.25	5	Died
F	*P. falciparum*	−	4.0	14¾	Macular rash over entire body; bloody vomitus	212	Not done		3.70	1	Mod.
G	*P. falciparum*	−	5.0	28	Blood in stool and urine	Not done	Not done		5.00	4	Severe
H	*P. vivax*	−	3.33	4½	Gross hemorrhage from bowel and petechiæ of skin of left flank, axillæ and buccal mucous membrane	129	2	5	2.17	5	Severe
I	*P. vivax*	+	4.0	Approx. 24	Petechiæ on skin of arms, legs, abdomen	160	"Normal"		3.85	5	Mod.
J	*P. vivax*	+	0.67	Not known*	Bilateral subconjunctival hemorrhage	216	3	2	4.44	4	Mild

* Noted 4 days later.

laboratory findings were as follows: leukocytes, 13,450 per c.mm. of blood; erythrocytes, 3,700,000 per c.mm. of blood; hemoglobin, 80%; blood film positive for *P. falciparum*. Quinine therapy was instituted, the patient receiving 2 gm. orally at 1 A.M., 1 gm. at 7 A.M., and 1 gm. at 1 P.M. At 3:45 P.M., $14\frac{3}{4}$ hours after the institution of the quinine therapy, the patient vomited 2 ounces of bloody material, passed urine containing erythrocytes, and a macular rash appeared over the entire body; areas of "redness" were noted on the right cheek. He also had a shaking chill, tinnitus aurium, and deafness. The platelet count at this time was 212,000 per c.mm. of blood. Quinine was discontinued and the patient was placed upon atabrine therapy, the hemorrhagic manifestations ceasing in 1 day and all symptoms clearing up within 4 days. This is a case of non-thrombocytopenic purpura occurring in a patient with malaria following the institution of quinine therapy.

CASE C. A 22 year old, white soldier was admitted on Jan. 4, 1943, with fever, chills, headache, dyspnea on exertion, abdominal cramps, and loss of appetite. He also complained of a dry, hacking cough and night sweats of 3 months duration. In June 1942, while the patient was stationed at a jungle position, he had symptoms of malaria and treated himself with quinine, taking 3 gm. daily for 7 days without any untoward effects. The patient had 2 attacks of malaria diagnosed by blood film examination in September and in November 1942. From Dec. 14, 1942, to Jan. 2, 1943, the patient took 0.6 gm. of quinine daily without any signs of sensitivity. On Jan. 3, 1943, he took 2.6 gm. of quinine in a single dose because he believed that his symptoms were due to malaria. On Jan. 4, 1943, when the patient entered the hospital, petechiæ were found scattered in the skin over the malleoli and anterior aspects of both lower extremities, the thorax, and the upper extremities. The tonsillar pillars and pharynx were injected and the postcervical lymph nodes were enlarged. There were coarse râles in the apices of both lungs, epigastric tenderness, and the spleen was palpable. Roentgen ray examination of the chest was negative. *P. vivax* was found in the blood film. At the time of admission his platelet count was 24,000 per c.mm. of blood; erythrocytes, 4,650,000 per c.mm. of blood; and leukocytes, 7600 per c.mm. of blood, with a normal differential. The bleeding and coagulation times were normal. Quinine was discontinued, a course of atabrine treatment was instituted; 2 days after completion of atabrine therapy a course of plasmochin was started. The petechiæ had faded by the 3rd day of atabrine treatment. At the end of the week, the platelet count was 213,000 per c.mm. of blood and the patient made an uneventful recovery. This is a case of thrombocytopenic purpura secondary to the use of quinine in the treatment of malaria.

CASE E. A white soldier, age 22, was admitted on Jan. 29, 1942, with the chief complaints of muscular aching, malaise, frontal headache, shaking chill, fever, and repeated vomiting. In September 1942, the patient had been admitted to the hospital with a fever of undetermined origin which responded quickly to quinine therapy. Just 1 week prior to the terminal admission the patient had been discharged from the hospital after being treated for estivo-autumnal malaria. On his third and final admission the scleras were slightly icteric, the pharynx showed a diffuse hyperemia, and the spleen was palpable. No plasmodia were found on examination of the blood during this admission. He was given 2 gm. of quinine at midnight. The following day the patient passed bloody urine, vomited blood, and had tarry stools. His red cell count dropped to 2,950,000 per c.mm. of blood, hemoglobin to 50% (Sahli method). The white cell count rose to 19,000 per c.mm. of blood, with a differential of 80% polymorphonuclears and 20% lymphocytes. The platelet count was 49,000 per c.mm. of blood. A tourniquet test applied to the arm was negative. Quinine was discontinued, the patient was placed on atabrine routine, given infusions of saline with 10% glucose, 3 blood transfusions, and oxygen therapy. By the 6th day of his illness he developed severe oliguria, marked pulmonary edema, and expectorated bloody sputum. The patient died on Feb. 3, 1942. Autopsy revealed pulmonary edema, hemorrhagic nephritis, and perirenal hemorrhage. This is a case of thrombocytopenia with hemorrhage into the gastro-intestinal and urinary tracts following the use of quinine.

Comment. Although only 0.1% of the cases of malaria treated at Gorgas Hospi-

tal manifested hemorrhagic tendencies, these were of grave import, necessitating the placing of 4 of the 10 patients with purpura on the seriously ill list.

That this condition may be an allergic manifestation and not a simple toxic one is suggested by the fact that one-half of the patients who developed purpuric manifestations had received quinine previously without developing any untoward symptoms, the wide variations in the amount of quinine taken before the development of purpura, and the fact that the hemorrhagic picture in the patient who had not been treated and in those who were treated with quinine was similar.

Tuft[15] stated: "Drug allergy or idiosyncrasy refers to a condition of hypersensitiveness or allergy in which the administration of a medicinal substance in a quantity non-toxic for the average individual is followed by an unusual but characteristic reaction. This type of reaction is distinguished from that due to the toxic action of the drug by the fact that the latter produces symptoms which are an exaggeration of its physiologic action." The total amount of quinine which the patients received before developing purpura was never more than 5 gm. in divided doses and most times less. Thousands of patients took more quinine without developing purpura. This purpura, then, was not due simply to the toxic effect of quinine. Vaughan[16] stated that symptoms of drug allergy "may follow the first recognized or traceable contact with the drug. Usually there is history of previous administration of longer or shorter duration, often with an intervening period without the drug." This fits in very well with the history of our patients, many of whom received quinine over a prolonged period of time before the onset of purpura.

For these reasons it appears that purpuras arising in patients treated with quinine are expressions of allergy. The fact that in the absence of malaria some of the patients took quinine without any reaction, but developed the hemorrhages in the presence of malaria, may indicate that malaria itself can act as a sensitizing agent for the production of an allergy to quinine. Indeed, the appearance of purpura in cases of malaria in the absence of any antimalarial drug suggests that the plasmodium or its toxins may be capable of acting as an allergin. Conversely, it is conceivable that quinine may act as a sensitizer to the malaria allergin which may produce purpura. These are mere speculations which await investigation.

The occurrence of purpura in white Americans only in Gorgas Hospital, where a large proportion of the patients with malaria are native Panamanians and British West Indian Negroes, is puzzling. While some of the skin manifestations might have been overlooked in these groups of patients, certainly the severe visceral manifestations could not have escaped notice. Part of the answer may be that these native groups have not been exposed to the evil of sensitization by repeated dosage with quinine used in a so-called "suppressive" or "prophylactic" manner. It is the impression of some members of the hospital staff that allergic manifestations as a whole are less frequent in the native population groups than in the Americans.

Although quinine may be instrumental in causing a hemorrhagic diathesis, it may be given in untreated malaria complicated by purpura with good results, but by far the wiser course would be to use atabrine which, in over 2500 cases of malaria, was not associated with purpura.

The 2 deaths bring out an important point. Persons sensitive to antimalarial drugs run an additional hazard of death in malarious districts. It is the policy of the Medical Examining Board of Gorgas Hospital to declare such individuals unfit for tropical duty.

Summary. 1. In 10,000 consecutive cases of malaria treated at Gorgas Hospital there were 10 cases (0.1%) complicated by purpura. There was 1 case of purpura in a patient with untreated

malaria, but in 9 cases the purpura followed the use of quinine.

2. The incidence of purpura in cases treated with quinine was 9:7500 (0.12%).

3. There were no instances of purpura following the use of atabrine in over 2500 cases of malaria.

4. Purpura occurred as frequently in cases of tertian malaria as in estivo-autumnal malaria.

5. The purpuras were evenly divided between thrombocytopenic and non-thrombocytopenic varieties.

6. The regions of the body affected were the gastro-intestinal tract, genito-urinary tract, skin, conjunctiva, and respiratory tract, in that order.

7. The withdrawal of quinine was of value in those cases in which the purpura was due to quinine, but in the patient without previous antimalarial therapy quinine was used successfully despite the presence of purpura.

8. Other measures used in the treatment of malaria patients with purpura were the institution of an atabrine routine, intravenous infusions of saline and glucose, blood transfusions, plasma transfusions, alkalinization of the patients, oxygen therapy, and the use of calcium gluconate and vitamin K.

9. The purpuric manifestations persisted for from 1 to 5 days after the institution of measures to control them. The complication was a serious one, necessitating the placing of 40% of the affected patients on the seriously ill list. Two patients died.

10. All patients affected were white American males, mostly belonging to the younger age group. No purpura occurred in the native population which made up a large number of the malarial patients.

11. We suggest that purpura due to quinine may be an allergic phenomenon and not simply a toxic manifestation.

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THE BLOOD PROTEIN TYROSINE REACTION IN MALARIA, ACUTE EPIDEMIC HEPATITIS, AND CERTAIN OTHER DISEASES

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In the past, several seroflocculation tests have been described for the diagnosis of malaria.[1,3,6] Such tests, if proved reliable, would be a useful diagnostic aid, particularly in patients who have clinical evidences of malaria, but repeatedly negative thick blood films. One of the most easily performed of the seroflocculation tests is the protein tyrosine reaction described by Proske and Watson[6] in 1939. The purpose of this investigation was to evaluate the blood protein tyrosine reaction in the diagnosis of malaria and certain other diseases, including acute epidemic hepatitis (acute infectious hepatitis, acute catarrhal jaundice, acute infectious jaundice, etc.).

Proske and Watson have reviewed the literature on seroflocculation tests in malaria and other diseases, and the reader is referred to their article for details. Although differences of opinion exist concerning the significance of these tests, and various theories have been advanced to explain the mechanism of abnormal flocculation, available evidence indicates that a positive reaction may occur in any disease in which there is a disturbance of serum globulin. Proske and Watson reported that the protein tyrosine test was elevated in patients with malaria. In normal persons the protein tyrosine test varied between 50 and 80 (arbitrary units), whereas in patients with malaria the range was 105 to 280 or higher. They found blood protein tyrosine elevated in 97% of cases of clinical malaria, whereas positive thick blood smears were obtained in only 82% of the same cases. A rise in blood protein tyrosine before the appearance of clinical symptoms in 1 patient indicated that the test might be useful in predicting a relapse of malaria.

Technique. According to Proske and Watson, the protein tyrosine reaction is based on the fact that "proteins possess a chromogenic property which can be measured quantitatively against the color produced by pure tyrosine in the presence of a phenol reagent. This chromogenic value is constant for a given protein and the intensity of the color produced can be used as a measure of the amount of the protein examined." The color is developed by means of a phenol molybdate-tungstate reagent, which presumably reacts with the phenol group of tyrosine in the protein. The precipitated protein is thought to be euglobulin. We have used the method described by Proske and Watson.

Reagents. 1. Sodium sulfate solution (14%): dissolve 70 gm. of c.p. anhydrous sodium sulfate in 300 ml. of freshly distilled water and make up to 500 ml. at 37° C. This solution is stored in an incubator at 37° C. and keeps indefinitely.

2. Sodium hydroxide solution (5 N): dilute saturated, carbonate-free sodium hydroxide solution to 20% with distilled water.

3. Tyrosine standard solution: dissolve 200 mg. of tyrosine (Pfanstiehl) in 1000 ml. of 0.1 N hydrochloric acid, which makes a solution containing 1 mg. of tyrosine per 5 ml. of 0.1 N hydrochloric acid. This stock solution is kept in a refrigerator.

4. Phenol reagent of Folin and Ciocalteu:[2] into a 1500 ml. Florence flask introduce 100 gm. of sodium tungstate ($Na_2WO_4.2H_2O$) 25 gm. of sodium molybdate ($Na_2MoO_4.H_2O$), 700 ml. of distilled water, 50 ml. of 85% phosphoric acid (H_3PO_4) and 100 ml. of concentrated hydrochloric acid. Reflux gently for 10 hours. Add 150 gm. of lithium

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sulfate (Li_2SO_4), 50 ml. of distilled water and a few drops of bromine water. Boil the mixture for 15 minutes without the condenser to remove excess bromine. Cool, dilute to 1000 ml., and filter. Freshly prepared reagent should have no greenish tinge, but, if this develops with age, the solution can be made usable by addition of a few drops of bromine water, boiling for a few minutes to remove excess bromine, and stopping when the solution is golden yellow.

Procedure. Measure 3 ml. of 14% sodium sulfate solution into a small test-tube and add 0.1 ml. of unheated, clear, non-hemolyzed serum. Mix by inversion, stopper the tube, and place in an incubator at 37° C. for at least 3 hours. As a matter of convenience the mixture may be left in the incubator overnight. At the end of incubation centrifuge the mixture at about 1500 r.p.m. for 10 minutes. Completely remove the supernatant fluid with a pipette and wash the precipitate twice with fresh sodium sulfate solution by centrifugation. Dissolve the washed precipitate in 1.75 ml. of distilled water and add 0.1 ml. of 5 N sodium hydroxide.

The standard is prepared by placing 2 ml. of tyrosine solution, 5 ml. of distilled water and 1 ml. of 5 N sodium hydroxide in a

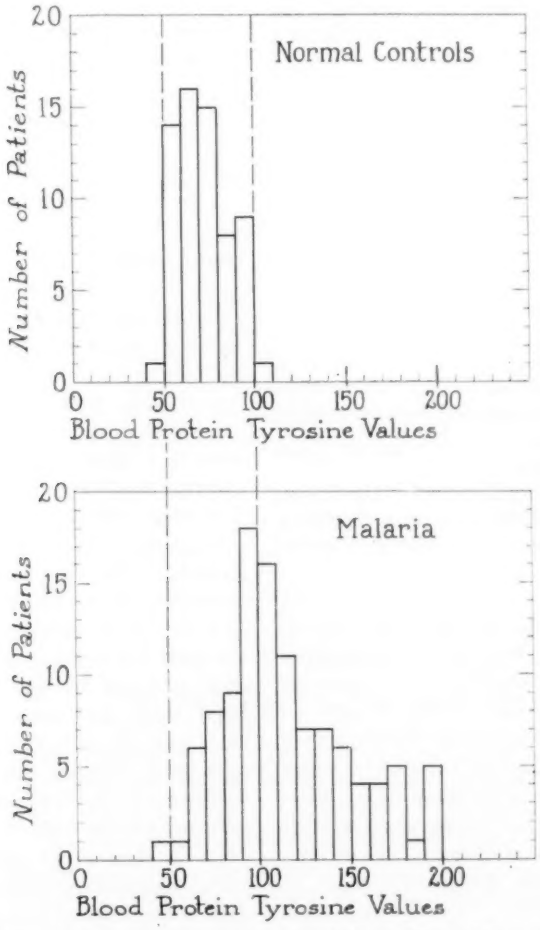

CHART 1.—Comparison of blood protein tyrosine of malaria patients with normal individuals. The 2 broken vertical lines show the normal variation of the test. Although the average value for patients with malaria was increased, nevertheless 40% of the values were in the normal range.

20 ml. graduated tube. Heat unknown and standard in boiling water for 10 minutes and allow to cool. Add to the unknown 0.15 ml., and to the standard 1.5 ml. of phenol reagent, and make up the standard to the 20 ml. mark with distilled water. The unknown may be compared with the standard in a colorimeter or with a series of substandards prepared by diluting the standard with suitable amounts of distilled water.

The results were expressed in arbitrary units, rather than in mg. because the test measures a protein fraction or fractions, the exact nature of which is unknown; namely, the fraction precipitated by 14% sodium sulfate solution. The results have been calculated according to the following formula: $\frac{\text{Standard}}{\text{Unknown}} \times 100 =$ protein tyrosine. This procedure is sufficient for clinical purposes, where interest is in a deviation from normal and not necessarily in absolute values.

Results. In order to determine normal variations of the test 60 determinations of blood protein tyrosine were made on 33 healthy young men, 20 to 35 years of age (Chart 1). The average blood protein tyrosine value was 70. Because values varied from 50 to 100, these limits were chosen as the normal range, and any test above 100 was considered abnormal. Duplicate tests on the same sample of serum checked within 5%, although tests done on the same person sometimes varied as much as 20 units on different days, but always within normal limits. Determinations were made before and after meals, at various times during the day, after exercise, and following exposure to cold, but these procedures had no effect upon the test. In order to study the effect of elevation of temperature on the test, determinations were made on 2 patients with chronic gonococcal urethritis, who were being treated in the fever cabinet. No change was observed during fever therapy, but 1 patient became slightly jaundiced (icterus index 15) 4 days later, and protein tyrosine rose from 83 to 108, returning to normal after 7 days.

Malaria. Protein tyrosine determinations were made on 110 patients with clinical evidences of *Plasmodium vivax* malaria (benign tertian) and positive blood smears. No cases with *P. falciparum* or *P. malariæ* infections were studied. All patients were young, white men 18 to 30 years old, who previous to military service in the tropics were in excellent health and had not had malaria. During the course of their duties they were in a highly malarious district under combat conditions for a period of about 4 months before they were evacuated to a temperate region in which there was no malaria. The first cases of malaria occurred at the end of 2 weeks in the tropics, and the peak incidence was reached at the end of 3 months, after which the disease persisted for as long as the troops remained in that area. They were treated with quinine and atabrine upon appearance of symptoms, and after the first few weeks most of them received suppressive treatment consisting of atabrine 0.1 gm., twice a day every 3rd day. In most cases suppressive treatment was stopped soon after evacuation. Protein tyrosine determinations were started 3 months after the patients had moved to a temperate climate. As soon as plasmodia were discovered in thick blood films, blood was drawn for the first protein tyrosine determination; other determinations were made at intervals of 1 week. Three determinations were made in most cases.

Chart 1 shows the results which are plotted with the control series for purposes of comparison. The average value was

TABLE 1.—VALUES OBTAINED AT VARIOUS TIME INTERVALS

Time interval	No. cases	Mean protein tyrosine (arbitrary units) with the standard error
1st 2 weeks	58	125 ± 4.99
2nd 2 weeks	22	113 ± 3.86
3rd 2 weeks	25	90 ± 2.70
Last 2 months	27	64 ± 3.27

125, which is definitely abnormal, but a study of the distribution of the readings showed that 40% of them were in the normal range. This means that a significant proportion of patients who were tested when malaria parasites were demonstrable in the blood stream had a negative tyrosine reaction.

Malarial Relapse. The relapse rate during the period of investigation was 35%. That is to say, of the 110 patients, 38 returned to the hospital within 3 months with signs of clinical malaria and positive blood smears. This fact raised the question of the value of the test in predicting relapse. Did patients with an increased blood protein tyrosine relapse sooner than patients with normal values? Was there a tell-tale increase just before a relapse?

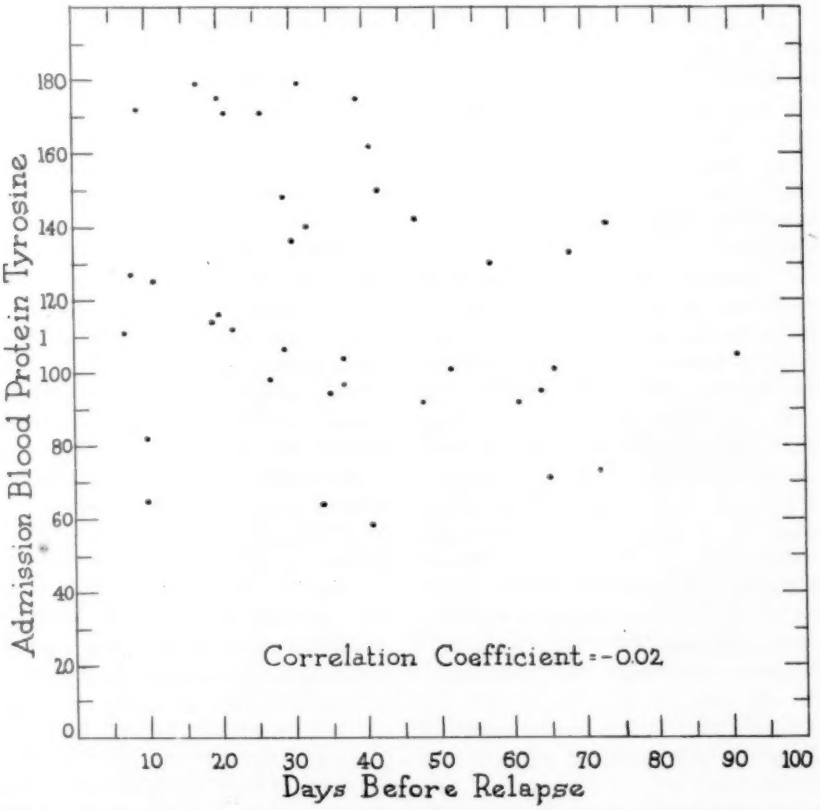

CHART 2.—Scatter diagram of the blood protein tyrosine of 110 patients on their first hospital admission, and the number of days elapsing before readmission to hospital because of a relapse. There is no significant association between the 2 sets of observations.

Comparison of results obtained early in the investigation with those obtained later (Table 1) showed that the protein tyrosine reaction gradually returned to normal in most patients. In the first 6 weeks there was a gradual fall in the mean value from 125 to 64, at which level the tests remained stationary during the rest of the experimental period; a matter of 3 months.

Chart 2 gives the answer to the first part of the question. This chart is a scatter diagram of admission protein tyrosine readings and the number of days elapsing before readmission to hospital because of a relapse. These readings are

obviously so widely scattered that there is no significant association between the 2 sets of observations. The correlation coefficient for the data is −0.02, which indicates a lack of correlation because it approaches closely to zero. In other words, admission blood protein tyrosine values, whether high or low, were not useful in predicting relapse.

In answer to the second part of the question it may be said that only 8 patients (22.8%) of those readmitted for relapse had an increased blood protein tyrosine. The other patients had normal values on readmission. Thus it must be concluded that the blood protein tyrosine reaction is not helpful in predicting malarial relapses.

Acute Epidemic Hepatitis. A question arose, during the course of this work, as to the behavior of the protein tyrosine reaction in diseases other than malaria. Of the diseases which were studied, the only one in which the protein tyrosine content of blood was frequently elevated was acute epidemic hepatitis. Twenty-seven patients were examined in whom the diagnosis of acute epidemic hepatitis had been made on the basis of clinical findings plus an increased icterus index (Table 2). In 11 cases cephalin flocculation tests were also done, but no attempt was made to investigate liver function in detail. All were young adult soldiers, 18 to 30 years old. The causative agent of the disease in this group of patients was not discovered.

Readings were made at weekly intervals, but some of them have been omitted in order to shorten the table (Table 2). Enough have been included, however, to show the behavior of the protein tyrosine and icterus index in each case.

Elevation of blood protein tyrosine occurred sometime during the disease in all except 2 patients (Cases 9 and 12), 1 of whom had a 1+, and the other a 3+ cephalin flocculation test. There is no apparent explanation for these 2 cases.

Whenever the protein tyrosine was over 100 the cephalin flocculation reaction, in all cases tested, was 4+. Two and 3+ cephalin flocculation tests were seen in cases with normal protein tyrosine values, and also in a few apparently healthy individuals.

Miscellaneous Diseases. Blood protein tyrosine was determined in a variety of diseases (Table 3), in most of which the protein tyrosine was not increased. However, an elevation of protein tyrosine occurred in 2 cases of enteric fever, and 1 each of lobar pneumonia, meningococcic meningitis, and acute infectious mononucleosis. With the exception of the case of lobar pneumonia, which showed a persistent and marked elevation, the increase in protein tyrosine was transient and moderate. Whether or not this increase was significant can only be determined by further study.

The patients with chronic calculous cholecystitis (pathologic diagnoses) were slightly jaundiced, but at operation no stones were found in either common or hepatic bile ducts.

Discussion. As stated earlier, the original purpose of this investigation was to determine the usefulness of the blood protein tyrosine reaction in the diagnosis of malaria. The results show that the test was not of diagnostic value in the particular group of patients studied, and under the experimental conditions which prevailed. This is clearly indicated by the fact that many patients had a normal blood protein tyrosine level at the same time that large numbers of plasmodia could be easily demonstrated in peripheral blood. It was also impossible to predict a relapse by means of the test.

Although these findings seem to conflict with those of Proske and Watson, the discrepancy is probably not as great as might appear at first sight. It is important to note that the 2 investigations were carried out on 2 different groups of patients and under different circumstances. Proske and Watson tested patients who lived in an endemic area and probably suffered from chronic malaria. In contrast, our patients had relatively acute

TABLE 2.—DATA ON 27 CASES OF EPIDEMIC HEPATITIS

Case	Hosp. days	Date, 1943	Icterus index	Protein tyrosine (arbitrary units)	Cephalin floc.	Liver	Last attack of malaria	Remarks
1	138	Mar. 22	144	..	...	Large tender	Jan. 1943	Jaundice present 2 mos. before protein tyrosine test; May 24, discharged "cured" before another reading was made
		Apr. 7	55	234				
		May 1	23	156				
		May 10	9	99				
		May 17	7	115				
2	85	May 8	21	217	...	Large tender	Jan. 1943	Relapse of jaundice June 1
		May 31	10	119				
		June 7	59	166				
		June 21	23	230	++++			
		June 28	15	172	++++			
		July 5	15	133	++++			
		July 26	5	75				
3	80	Apr. 19	73	250	...	Large tender	Dec. 1942	June 9, discharged "cured"
		May 17	10	142				
		June 7	9	105				
4	70	Apr. 23	162	135	...	Large tender	Nov. 1942	
		May 3	109	83				
		June 14	25	82	+			
		June 22	14	103				
		June 28	10	88	+			
		July 12	..	69				
5	68	June 3	16	77	...	Normal	None	Jaundice in July, Aug., Dec. 1942; April 1943
		June 21	18	99				
		June 28	18	104	++++			
		July 12	21	80				
6	51	June 10	48	85	...	Normal	None	
		June 21	80	100	++			
		July 5	40	72	++			
		Aug. 1	8	75				
7	50	June 7	19	97	...	Large tender	None	
		June 24	7	120	++++			
		July 5	10	110	+++			
		July 28	..	41				
		Aug. 2	3	62				
8	48	May 21	6	133	...	Large tender	None	May 21, discharged "cured"; June 23, readmitted with recurrence of jaundice; July 31, 2nd discharge
		June 28	36	175	++++			
		July 5	14	159	++++			
		July 26	10	128				
9	35	June 14	24	67	+++	Normal	None	
		June 21	27	83				
		July 5	10	56	++			
10	33	Apr. 7	44	144	...	Large tender	None	
		May 5	17	102				
		May 10	10	98				
11	31	May 3	50	115	...	Large tender	None	Transferred to another hospital while still ill
		May 10	25	90				
		May 17	21	130				
12	30	June 28	32	71	+	Normal	None	Deep jaundice with normal liver, cephalin flocculation and protein tyrosine test
		July 3	96	88				
		July 5	136	69	+			
		July 12	90	81				
		July 26	8	56				
13	30	Mar. 7	43	112	...	Large tender	None	Mar. 20, discharged.
14	28	June 11	56	68	...	Large tender		
		June 21	15	108				
		July 5	8	58	+			
15	28	May 22	60	125	++++	Large tender	May 19, 1943	Malaria and jaundice simultaneously
16	24	July 9	130	121	...	Large tender	None	
		July 13	40	94				
		July 26	10	64				
17	25	June 21	9	121	...	Large tender	None	Skin and sclera jaundiced
		July 27	4	127				
18	14	Apr. 20	20	126	...	Large tender	None	May 4, discharged "cured"
19	14	May 17	28	108	...	Large tender	None	
		May 24	16	53				
		May 27	11	64				
20	14	May 17	20	95	...	Large tender	None	
		May 22	40	115	++++			
		May 27	..	68				
21	13	May 5	60	106	...	Normal	None	
		May 10	48	94				
22	11	July 22	30	128	...	Large tender	None	
		July 26	12	77				
		July 31	10	75				
23	10	July 21	40	104	...	Tender	None	
		July 29	10	76				
24	9	May 11	7	132	...	Large tender	None	
		May 17	7	100				
25	8	Apr. 7	20	116	...	Tender	None	
26	7	June 25	4	115	...	Tender	None	Skin and sclera jaundiced
27	5	May 14	4	125	...	Tender	None	Skin and sclera jaundiced

TABLE 3.—MISCELLANEOUS DISEASES

Case	Diagnosis	Date, 1943	Protein tyrosine (arbitrary units)	Remarks
1	Chronic calculus cholecystitis	July 21	76	Icterus index 21; cephalin flocculation negative; bile ducts and liver normal at operation
2	Chronic calculus cholecystitis	July 22	75	Bile ducts and liver normal at operation
3	Chronic calculus cholecystitis	May 7	70	Bile ducts and liver normal at operation
4	Fever therapy for chronic gonorrhea	June 17	72	Before fever therapy
			76	After fever therapy
		June 23	90	
5	Fever therapy for chronic gonorrhea	June 17	83	Before fever therapy
			90	After fever therapy
		June 22	108	Patient jaundiced, icterus index 15
		July 1	83	Jaundice disappeared
6	Lobar pneumonia (Type I pneumococcus)	May 7	135	First reading obtained 4 days after crisis
		May 13	157	
		May 17	61	
7	Bronchopneumonia	May 8	91	"Atypical pneumonia"
		May 17	69	
8	Enteric fever	May 8	85	Mild case; blood culture, *B. typhosus*
		May 17	125	
		May 24	69	
9	Enteric fever	May 8	67	Mild case; blood culture, *B. typhosus*
		May 14	81	
		May 21	107	
		May 24	55	
10	Enteric fever	May 8	76	Mild case; blood culture, *B. typhosus*
		May 10	76	
11	Enteric fever	May 6	117	Mild case; blood culture, *B. paratyphosis A*
		May 17	84	
12	Meningococcic meningitis	May 8	81	
		May 10	99	
		May 17	87	
		May 27	81	
13	Meningococcic meningitis	May 22	70	
		May 27	56	
		May 31	82	
14	Meningococcic meningitis	July 5	102	
		July 12	94	
15	Influenza	May 17	98	Clinical diagnosis
16	Dengue fever	...	60	Clinical diagnosis
17	Acute pharyngitis	May 13	72	*Strep. pyogenes* and *Neisseria catarrhalis*
18	Acute tonsillitis	May 20	84	Alpha hemolytic streptococcus
19	Scrub typhus fever	June 16	73	Convalescent
		June 23	96	
20	Acute infectious mononucleosis	May 17	85	Heterophil agglutination 1:1280
21	Acute infectious mononucleosis	May 17	121	Heterophil agglutination 1:1280
		May 24	83	
22	Acute infectious mononucleosis	May 14	62	Heterophil agglutination 1:1280
		May 22	85	
23	Acute infectious mononucleosis	May 24	80	Heterophil agglutination 1:1280
		May 27	72	
24	Lymphogranuloma venereum	May 21	57	Virus isolated in eggs
		June 5	51	
25	Hookworm	May 7	83	Heavy infection
26	Hookworm	May 29	51	Moderate infection
27	Ascaris and whipworm	May 25	62	Moderate infection
28	Polycythemia vera	June 24	95	
		June 28	57	
		July 5	91	

malaria and were studied in a temperate, non-malarious region. Proske and Watson's subjects were exposed to reinfection while ours were not, since they were tested at least 3 months after their last possible exposure to infected mosquitoes. In the early part of the investigation, the blood protein tyrosine was high in many of our patients and it is possible that, if they had been studied immediately after leaving the malarious district, the elevation would have been higher and present in many more cases. The natural tendency of protein tyrosine to return to normal levels, which has been demonstrated in this paper, may well have been more obvious in our patients than in those that Proske and Watson studied.

It is apparent then that the seeming disparity of the 2 sets of observations may in reality indicate an important feature of malaria. If the blood protein tyrosine is increased in patients studied in endemic areas who are subject to reinfection, and not in patients who have been removed from such areas, then some alteration in blood proteins has occurred, the nature of which is as yet unknown. Comparable observations have been reported by Kopp and Solomon,[5] who found that in therapeutic malaria there is a transient impairment of liver function which disappears within 3 to 6 weeks after termination of malaria.

The observations in acute epidemic hepatitis suggest that determination of blood protein tyrosine may be a helpful laboratory procedure in the study of this disease. Presumably the test should be of help in studying other disorders of the liver and biliary tract, but unfortunately such a study was not possible because of lack of suitable clinical material in this hospital.

Summary. 1. Blood protein tyrosine (euglobulin) level was studied in patients with relatively acute malaria (*P. vivax*) 3 months after they had left the malarious district.

2. In these patients, and under the condition of the study the test was of limited diagnostic value, because 40% of those with positive blood films had a normal blood protein tyrosine. It was not of value in predicting relapses.

3. Elevated readings in patients with malaria returned to normal within a few months.

4. Blood protein tyrosine was elevated in many cases of acute epidemic hepatitis.

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THE URINARY EXCRETION OF METHIONINE IN LIVER DISORDER

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The amino acid methionine, $CH_3.S.CH_2.CH_2.CH(NH_2).COOH$, has recently gained clinical recognition as a therapeutic agent in toxic hepatitis.[3,8,9] The possibility of its usefulness in other sorts of liver disease has been claimed by some[8] and denied by others.[2,4,13] Therapeutic use of methionine is founded on experimental studies of numerous workers, among them Miller, Ross and Whipple,[20] Himsworth and Glynn[14,15] and György.[11] The latter, based on his results with dietary experiments in rats, recommended the use of methionine as an adjuvant in the prevention and in the treatment of human liver disease. Du Vigneaud[23] demonstrated that methionine provides free methyl groups for the synthesis of choline and that it is of significance to sulfur and fat metabolism and to the problems of trans-methylation in the organism. The effectiveness of methionine in counteracting post-traumatic nitrogen loss in burned rats[6,7] may constitute another property of this substance.

Beattie and his co-workers[3] observed the beneficial effect of methionine in carbon tetrachloride poisoning and noticed the excretion of an excessive amount of urinary sulfur (equivalent to 65% of the sulfur given as methionine). They concluded that "the intimate cause of the liver disturbance induced by carbon tetrachloride is an abnormal metabolism of methionine and related compounds; and that in their patient it was specifically the administration of methionine which prevented further liver damage."

The present report deals with preliminary findings obtained in a study of the urinary excretion of methionine in various liver disorders.

First, the rate of the urinary excretion of methionine ingested by normal individuals orally was studied, and changes in urinary excretion due to the form of the absorbed methionine, either as crystals or as tablets containing a binder of unknown constitution, were investigated. Second, as renal impairment often accompanies liver disease, it was determined to what extent nephrosis and changes in urine volume would affect urinary methionine concentration.

Once these factors were known, methionine was given under various nutritional conditions and at various stages of liver disease to a patient with infectious hepatitis and to a patient with hepato-lenticular degeneration.

Materials and Methods. 1. *The Patients.* (*a*) Control investigations were done on young (30, 28, 32 years) healthy individuals who were doing their customary work in the laboratory during the experiments but adhered strictly to the necessary nutritional restrictions. In 1 instance a patient who was convalescent from severe burns was used as a control because his nutritional status at the time of the experiment was not significantly impaired and there was no evidence of liver disease.*

(*b*) The patient suffering from nephrosis was a 46 year old white female.† Albuminuria and edema had been present for 1½ years in this patient, whereas urine examinations prior to that period had been negative. The serum proteins in the past 1½ years varied from 4.5 to 3.5 gm. per 100 cc. and the

* Dr. F. H. L. Taylor's permission to use data obtained by his group on this patient is gratefully acknowledged.

† Patients (*b*) and (*d*) were private patients of Dr. H. Blotner whose coöperation in allowing study of these subjects is gratefully acknowledged.

albumin-globulin ratio was inverted. Cholesterol values were consistently around 600 mg. per 100 cc. of plasma. During the past year the patient had been kept on a high protein diet and was accustomed to weigh all her food as well as to measure her fluid intake and output. She was leading a semi-ambulatory life, doing some housework. During the experiment she was seen once a week and her drug, food and fluid intake was recorded with particular care.

(*c*) The patient with hepatolenticular degeneration has been described previously.[16,17] He was a white boy of 19 having shown symptoms of hepatolenticular degeneration during several years. His liver function had been followed over a period of 14 months under various diets and it had been found that episodes of liver dysfunction could be provoked by restricting the dietary protein. The studies on methionine excretion in this patient were performed during such a period of induced hepatic disturbance.

(*d*) The patient suffering with infectious hepatitis was a white male of 38. He had always been healthy until March 1945, when, after the usual prodromata marked jaundice, right upper quadrant distress and enlargement of the liver appeared. Under high protein and vitamin diet, and bedrest the symptoms regressed within 6 weeks but 1 month later jaundice recurred with an icteric index of 100, 3+ bile in the urine and a 3+ cephalin flocculation. The stools were always of fairly normal color. The response to the dietary treatment was unsatisfactory and the general condition of the patient deteriorated, while the liver edge descended below the umbilicus. Beginning on Aug. 12, 1945, 5 gm. of methionine were given by mouth every day and the dose was later increased to 10 gm. For technical reasons the study of methionine excretion was begun only on September 7. Subjective improvement had been perceptible about 1 week earlier, while liver enlargement and laboratory findings remained unchanged. During the actual period of the experiment, the liver regressed to normal size and the icteric index fell. The cephalin flocculation became 2+. Methionine was discontinued after a total dose of 483.6 gm. had been given. During the entire period of observation the diet had remained constant, the patient being hospitalized and a special dietitian being assigned to control his intake of food.

2. *Diets and Method of Methionine Administration.* It was kept in mind that various proteins of the diet contain different amounts of methionine. Methionine values of the usual constituents of hospital diets were not available and analysis of alimentary methionine was impossible for technical reasons. As a satisfactory compromise the sources of protein in all patients during the experiments were limited to casein, lean meat (lamb, beef and chicken) and the proportions of all of these constituents were kept fairly constant each day. The vegetable rations in each case were kept at comparable levels. Protein values were calculated from food tables.[5] Regardless of changes of the amounts of proteins necessitated by the experiments, the diets were maintained at constant caloric levels by adding, in the case of low protein diets, corresponding amounts of carbohydrates and fat to make up for the omitted protein.

The dl-Methionine was given in the form of "Meonine"* tablets (containing 0.3 gm. of dl-methionine and a binder, the nature of which was unknown) in the case of the normal subjects, the patient with hepato-lenticular degeneration and in the form of chemically pure crystals in the other patients. Unless otherwise specified the daily doses were fractionated into small amounts given every 3 hours from 8 A.M. to 8 P.M. in fruit juice or in water.

In the experiments on the variation of methionine excretion in normal subjects, the substance was given to 4 normal fasting individuals in the form of "Meonine" tablets with 200 cc. of water at 9 A.M. At 10 A.M. another 200 cc. of water were given. The urine was collected during the 12 hours preceding the experiment and its methionine content was measured. Urine was again collected at 12 NOON, 3 hours after the ingestion of methionine, and the methionine contained in this 3 hour specimen was again determined. The same experiment was repeated on the same subjects several days later, using methionine crystals free of any binder.

* Part of the methionine used was supplied by Wyeth, Inc., through the coöperation of Dr. R. M. Johnson.

The excretion curves studied by Albanese[2] in normal persons were studied in 6 normal individuals, by measuring their urinary methionine before ingestion of 1.5 gm. of methionine ("Meonine" tablets) and ½ hour, 1 hour, 2 hours and 3 hours thereafter. The amounts of fluid given during the experiment were identical to those used by Albanese.

in the form of tablets containing a binder or as powder by one and the same normal person are presented in Table 1. It appears that in some cases, methionine ingested in the form of pure crystals increases the amount of methionine excreted in the urine in a given time interval more markedly than does the same amount of

TABLE 1

Subject	Urinary methionine: 12 hours before ingestion (mg./1 cc.)	Urinary methionine: 3 hours after ingestion (mg./1 cc.)
Effect of the Ingestion of 5 Gm. of Methionine in Tablets		
F. H.	0.13	0.45
S. C.	0.24	0.39
B. O.	0.15	0.35
G. H.	0.16	0.18 (after 6 hours 0.36)
Effect of the Ingestion of 5 Gm. of Methionine in Powder		
F. H.	0.11	0.60
S. C.	0.18	0.41
B. O.	0.17	0.60
G. H.	0.14	0.18 (after 6 hours 0.40)

3. *Methionine Determination in Urine and Feces.* In all experiments except those described above all urine was collected in 24 hour specimens. Urine was preserved with 50 cc. of 15% hydrochloric acid plus 1 cc. of a 10% alcoholic thymol solution, and kept in the refrigerator. Methionine determinations were done within 7 days. This is a safe period for the preservation of methionine according to a personal communication from Albanese. The method of Albanese[5] was used for urine methionine determinations. The same method was applied to fecal methionine after pulverization of the dried feces and resuspension of the material in distilled water.

4. *Other Laboratory Methods.* The total urinary nitrogen was determined by the macro-Kjeldahl method[21] and 10% of the nitrogen intake were allowed for fecal nitrogen loss.

The cephalin flocculation test was performed according to Hanger's[12] technique and prothrombin time determinations were done by a modification of Quick's method.[22] The icteric index was estimated by direct visual comparison of the serum to standards.

Results. 1. *Variations of Urinary Methionine Excretion Following Oral Administration of Tablets or Crystals.* Experiments on the excretion of methionine when taken

methionine, ingested by the same individual, in the form of tablets. It also appears that the amount excreted differs in different individuals. This point was further illustrated by repeating the excretion experiments of Albanese[5] in 6 normal individuals. While 4 showed excretion curves comparable to those found by Albanese, 2 repeatedly had markedly slowed and prolonged excretion. (One of these was G. H. of Table 1.)

2. *Methionine Excretion in a Normal Individual on Various Diets.* (Chart 1.) Albanese found that a normal adult "on a normal diet"[2] excretes from 200 to 500 mg. of methionine in the urine in 24 hours. This does not significantly change when the subject is placed on a low protein diet (3.5 gm. of N_2) or when he is ingesting an isocaloric, high protein diet (30 gm. of N_2). When methionine is added, while the diet is poor in protein, a slight increase of urinary methionine excretion occurs. This is enhanced when the dietary protein is increased. The urinary methionine excretion immediately fell when methionine intake was diminished. The nitrogen balance under the

conditions of this experiment was not changed by the addition of methionine.

3. *Methionine Excretion in Nephrosis.* (Chart 2.) During a control period of 7 days on a diet of 3000 Calories containing about 150 gm. of protein this patient excreted methionine in amounts comparable to those found in urine of a normal person. On 5 gm. of methionine tablets, the increase in urinary methionine was comparable to that observed in a normal person under similar conditions. On the

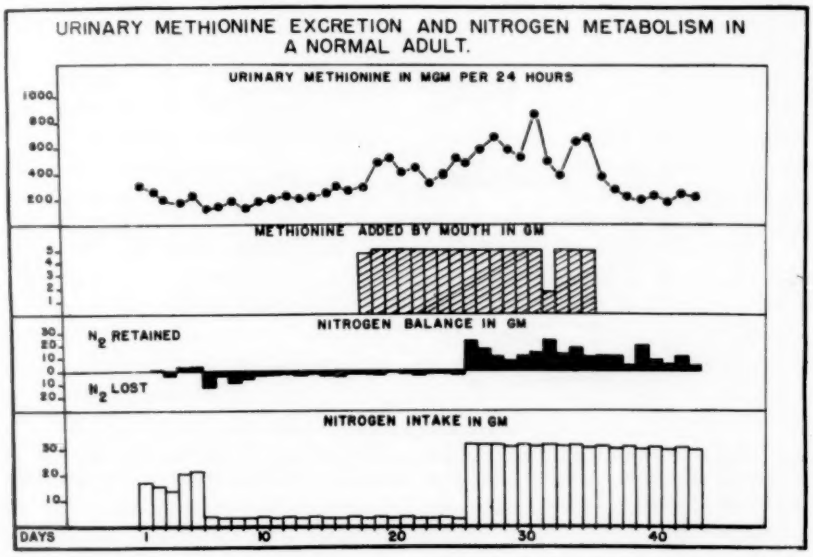

CHART 1.—Shows the changes in methionine excretion and nitrogen metabolism in a normal adult male of 30 on a diet of 3000 calories with varying amounts of protein.

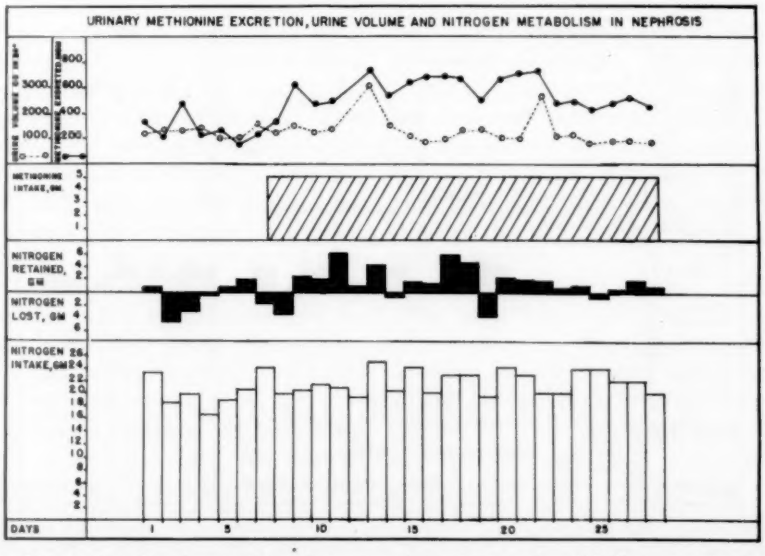

CHART 2.—Shows that there is no relation between urine volume and methionine excretion in a case of nephrosis maintained on a constant high protein diet.

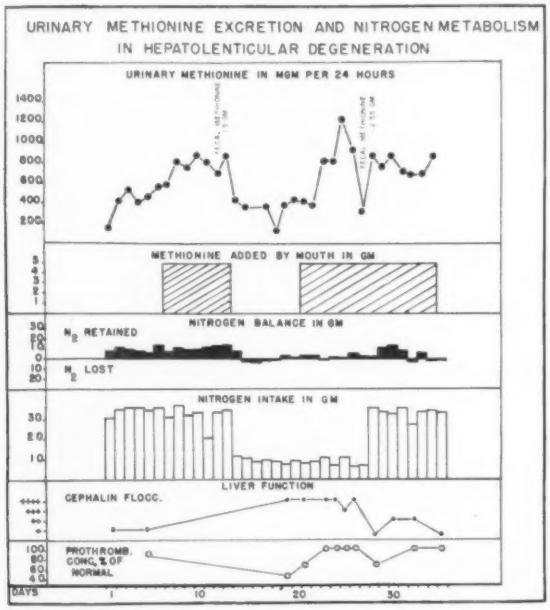

CHART 3.—Shows the changes in methionine excretion, nitrogen metabolism and liver function in a young adult male of 19 suffering from hepato-lenticular degeneration, maintained on a diet of 4000 calories with varying amounts of protein.

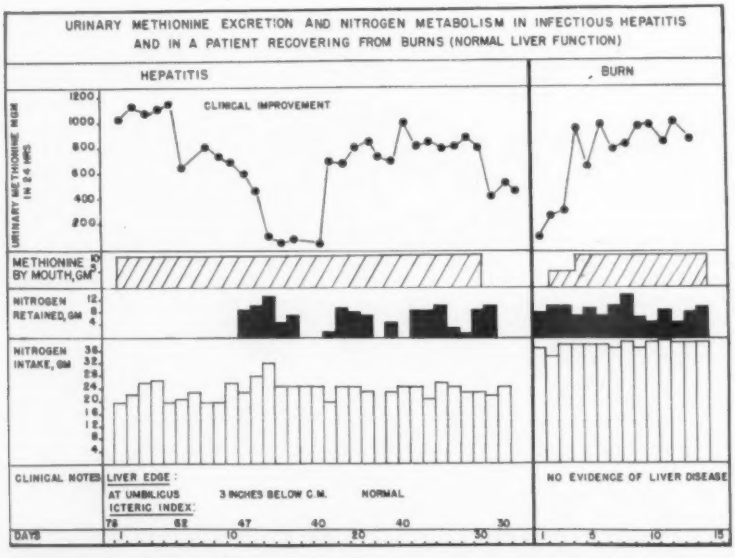

CHART 4.—Shows the changes of methionine excretion and nitrogen metabolism in a patient with infectious hepatitis during the period of recovery, on a constant high protein diet of 4000 calories. On the right side is shown the methionine excretion and nitrogen balance of a patient recovering from burns, on a constant high protein diet.

13th and on the 23rd day the urine volume was greatly increased following the injection of mercupurin. The changes of the methionine excretion did not parallel those of the urine volume. The nitrogen balance which varied somewhat during the experiment was more stable after the 20th day of the experiment. It is impossible to say whether methionine had anything to do with this change.

This experiment may be interpreted as meaning that the renal changes sometimes found in liver disease cannot be expected to affect significantly the urinary elimination of methionine.

4. *Methionine Excretion in Hepato-lenticular Degeneration.* (Chart 3.) In this patient acute liver failure followed the restriction of dietary protein which was reduced from 220 to 60 gm. while the total calories were maintained at 4000. In a preceding control period the administration of 5 gm. of methionine in tablet form daily had caused an increase of urinary methionine comparable or slightly higher than seen in the normal subject. During the low protein diet, when no methionine was given, 420 to 150 mg. of methionine were excreted, which is within the normal range. The addition of methionine to the low protein diet, at a time when liver function was poor, caused a more marked increase than that observed in the normal subject under similar conditions. This would have been even more accentuated had the patient not suffered from diarrhea which, at this point, nearly doubled his fecal methionine loss and greatly increased fecal nitrogen. The maximal methionine loss during this period was 3.75 gm. in 24 hours while it was only 2.4 gm. in 24 hours when methionine was given, together with a high protein diet and while liver function tests were normal.

5. *Methionine Excretion in Infectious Hepatitis.* (Chart 4.) In this patient methionine excretion studies were begun after he had received 5 gm. of methionine daily for 8 days and 10 gm. daily for 16 days. Clinical improvement had just begun when the study was started. Throughout the experiment the patient was taking a high protein diet. During the first 5 days of the experiment his methionine excretion was between 1050 and 1165 mg. per day while in a control subject this value remained below 1000 mg. although the protein intake of the control was higher and to a great extent derived from casein, therefore rich in methionine. There was no evidence of liver damage in the control subject who was recovering from burns. The urinary methionine values in the patient with hepatitis fell below normal as he improved and approached levels found in the control subject as the patient's condition became stabilized. The nitrogen balance was not changed.

Discussion. The only previous studies on urinary methionine excretion are those of Albanese[5] in normal subjects. However there is indirect evidence that in some conditions methionine loss in the urine is increased. Thus in the case of carbon tetrachloride poisoning Beattie *et al.*[3] found an increased excretion of unoxidized sulfur (about 65% of the amount of sulfur given as methionine). Miller[19] reported that the feeding of methionine to protein depleted dogs caused an increase in urinary organic sulfur amounting to 15 to 40% of the sulfur fed as methionine.

It is not known whether this methionine loss is due to the lack of certain components of protein, which might be necessary for the utilization of methionine as Gillman and Gillman[10] have suggested, or whether the failure of the organism to fully utilize methionine is due to an impairment of certain metabolic functions of the liver. This latter hypothesis seems to be supported by the findings here presented. Whereas, the high methionine excretion in the patient with hepato-lenticular degeneration (Chart 3) was accompanied by liver dysfunction and by protein deficiency, the same phenomenon was observed with hepatitis while dietary proteins were adequate. In Miller's dogs[19] the metabolic functions of the liver may well have been disturbed as serum phosphatase

and dye clearance may be impaired in dogs after relatively short times of protein starvation.[18] In Beattie's patient the diet contained sufficient protein.

Furthermore, it has been shown that liver disease interferes with the metabolism of other amino acids. Bernhart and Schneider[4] showed this to be true for tyrosine and the studies of Abels, Kupel, Pack and Rhoads[1] demonstrated that the administration of glycine no longer increased urinary creatin and creatinine excretion when liver disease was present, even though free methyl groups were made available by simultaneous administration of choline.

The finding of increased urinary (and fecal) methionine excretion in liver dysfunction may be of practical importance as it may signify a defect in the proper utilization of methionine. This total methionine loss in the only instance where fecal methionine was determined amounted to 74% of the amount ingested and in Beattie's[3] patient this amount was 65%. Larger therapeutic doses than those usually employed may therefore be needed, probably as much as 15 or 20 gm. a day. Some caution is indicated when elevating the dose, as it has been seen in this clinic that 30 gm. of methionine, taken in 1 single dose caused nausea and projectile vomiting. Some discouraging results reported with the therapeutic use of methionine for infectious hepatitis may have to be interpreted with caution[13,24] as much of the 5 gm. of methionine given may have been lost in urine and feces as methionine. It appears also important to start methionine therapy as early as possible, before liver impairment interferes with methionine utilization as seems to be suggested by our findings.

In studies dealing with methionine metabolism it should be kept in mind that the excretion in the urine of this amino acid is somewhat different, depending on the form in which it is given. The presence of a binder in tablets, such as in "Meonine," apparently delays absorption from the gastro-intestinal tract.

Summary and Conclusions. 1. Urinary methionine excretion in different subjects varies and is affected by the form (tablets or powder) in which methionine is given.

2. Urinary methionine excretion in 1 case was not influenced by renal changes of a nephrotic type nor by changes of the urine volume.

3. In 2 cases of liver dysfunction urinary methionine loss was found to be increased during the height of the disturbance and decreased as the patients improved. In 1 case this occurred independently of dietary factors.

4. Methionine seems to be lost in the urine in greater quantity during liver disease than normally and it seems desirable to use large doses as early as possible in the course of disorder of the liver.

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THE USE OF MOLYBDENIZED FERROUS SULFATE IN THE TREATMENT OF TRUE IRON DEFICIENCY ANEMIA OF PREGNANCY

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The possible rôle of various trace elements, especially copper, in speeding recovery from certain experimental nutritional anemias, has been studied by a number of investigators. Up to the present time, however, copper alone has been convincingly demonstrated to be important in this regard, bringing about a better utilization of iron and quicker hemoglobin regeneration in animals with anemia induced by subsistence on a milk diet.[5] Other elements such as manganese, cobalt and germanium have been reported to be ineffective.[12,13]

Although the function of copper in hemopoiesis has been amply confirmed, it has been emphasized that this element allows a better utilization of iron only when there exists a combined deficiency of iron and copper such as results when the diet is made up exclusively of milk.[3] Concerning its usefulness in clinical anemias, authoritative opinion is that medicinal copper is not necessary for treatment of anemias in man, with the exception of certain hypochromic nutritional anemias in young infants.[4,7]

As far as one can learn from a careful search of the literature, molybdenum is not among the trace elements which have previously been studied from the standpoint of possible potentiation or catalysis of iron in the treatment of iron-deficiency anemias. In experimental studies of a molybdenized ferrous sulfate, which were undertaken and, on completion, will be reported separately, early results suggested that treatment with this preparation accomplished an unusually rapid cure of milk-induced anemia in young rats. The present communication deals with preliminary clinical studies of the relative therapeutic efficacy of ferrous sulfate and of molybdenized ferrous sulfate* in hypochromic anemias in pregnancy.

Clinical Material.† Twenty-two cooperative, obstetric out-patients with true iron-deficiency anemia served as the clinical subjects of study. The diagnosis of true anemia was made in each of these patients on the basis of initial blood values that were below the minimum normal standards for pregnancy.

That the minimum normal values for hemoglobin and erythrocytes in the pregnant woman are substantially lower than those in the non-pregnant woman is now well established. This difference is attributed to the occurrence, during pregnancy, of a so-called physiologic anemia which does not respond to iron therapy, since it is not a true anemia but rather a hydremia. Bethell[2] believes that the lowest normal blood values for hemoglobin and erythrocytes in pregnancy are 11.3 gm. % and 3.70 million per c.mm., respectively. From their studies Adair and associates[1] conclude that the minimum standards for normal pregnancy are 10 gm. of hemoglobin, 3.36 million erythrocytes and 33% of packed cell volume. Wolff and Limarzi[15] state that the efficacy of iron therapy in

* Molybdenized ferrous sulfate is prepared by a special process, involving the co-precipitation of molybdenum sesquioxide and ferrous sulfate, with the production of a complex in which elemental molybdenum and ferrous iron are present in an approximate ratio of 1 to 15 parts, respectively. It was made available for clinical study in the form of tablets, each of which contained 3 mg. of molybdenum sesquioxide (approximately 2.5 mg. of elemental molybdenum) and 195 mg. of ferrous sulfate (approximately 40 mg. of ferrous iron). These tablets were analyzed for copper by spectrographic and colorimetric (dithiazone) methods. The results showed that this element was present to an extent not greater than 5 parts per 1 million.

† Clinical data were obtained from patients in the Obstetrical Clinic of the Orange Memorial Hospital, Orange, N. J., under supervision of the Obstetrical Department.

pregnant women with obviously true anemia—or with questionably true anemia in which hemoglobin and erythrocyte values are at or just below the minimum standards for pregnancy—may be predicted from the mean corpuscular hemoglobin concentration. According to the latter investigators, when this index is below the normal range of 32 to 36%, iron is indicated; when this index is normal, iron is contraindicated.

On initial examination, all of our 22 pregnant patients had hemoglobin values less than 10 gm. %; 21 had erythrocyte counts less than 3.36 million; one had an erythrocyte count of 3.8 million (with a hemoglobin value of 7.6 gm. %); all had subnormal mean corpuscular hemoglobin concentrations.

Method of Study. All laboratory studies were done by one special technician. Hemoglobin estimations were made with a Klett-Summerson photoelectric colorimeter; packed erythrocyte volume was determined by the modified Haden method; blood pipets, counting chambers and cover-glasses which were used had been certified by the U. S. Bureau of Standards.

Hematologic study before start of treatment consisted of hemoglobin and packed cell volume determinations, erythrocyte counts, total and differential leukocyte counts, and examinations of stained blood smears. Initial hematologic study of each patient was made during a pre-medication control period of at least 7 days. After treatment was begun, hemoglobin determinations and erythrocyte counts were made approximately at weekly intervals.

The 22 patients under study were divided into 2 numerically equal groups. Each patient in Group 1 received a daily dose of approximately 240 mg. of ferrous iron in the form of 6 tablets of ferrous sulfate; each patient in Group 2 received approximately the same daily dose of ferrous iron, plus 15 mg. of molybdenum, in the form of 6 tablets of molybdenized ferrous sulfate. Since it is now known that iron is clinically more efficacious in the bivalent rather than the trivalent form, precautions were taken to make certain that the iron content of tablets of both preparations remained in the bivalent state.

Supplies of medication, sufficient only for 2 weeks treatment, were regularly distributed to all patients. Prescribed dosage was adhered to in all cases, as far as could be determined from frequent inspection of supplies of distributed tablets and verification that estimated quantities of unused tablets corresponded with actual quantities.

Results. In Group 1 hemoglobin levels at start of treatment ranged from 7.6 to to 9.8 (average 9.1) gm. %; in Group 2, these ranged from 7.6 to 9.4 (average 8.9) gm. %.

Following treatment for approximately the same length of time in both groups of patients, the hemoglobin levels in Group 1 were between 10.6 and 11.8 (average 11.2) gm. %; in Group 2 between 13.2 and 14.2 (average 13.5) gm. %. The average duration of treatment and weekly gain in hemoglobin were 6.9 weeks and 0.27 gm. % in Group 1; 6.2 weeks and 0.74 gm. % in Group 2. The foregoing data are listed in Table 1.

A more critical analysis of these results is facilitated by graphs of individual and group rates of hemoglobin formation. These are presented in Charts 1 to 3, examination of which reveals that the patients of Group 2, treated with molybdenized ferrous sulfate, experienced an unusually efficacious therapeutic response. The rate of hemoglobin formation in all patients of this group seemed to follow a distinctive pattern in which increments in hemoglobin concentration occurred with uniform rapidity until normal levels were almost attained. On the contrary, all patients in Group 1, receiving the same dosage of iron (but in the form of ferrous sulfate) as those in Group 2, exhibited an initially satisfactory therapeutic response followed by a progressively slower rate of hemoglobin regeneration, until hemoglobin values—still subnormal—were unaffected despite continued treatment with the same dose of ferrous sulfate. Curves of individual and average response to treatment in Group 1, therefore, showed an initial upward trend but gradually leveled off and became plateau-like while hemoglobin values were still subnormal.

TABLE 1.—HEMOGLOBIN LEVELS AFTER TREATMENT WITH FERROUS SULFATE AND MOLYBDENIZED FERROUS SULFATE

Group 1.—Medication: Ferrous Sulfate

Case No.	Initial Hb. (gm. %)	Initial M.C.H.C.*	Weeks of treatment	Subsequent Hb. (gm. %)
1	9.4	26	6	11.4
2	9.0	29	7	11.2
3	9.0	29	7	11.6
4	9.4	28	7	11.0
5	9.2	24	6	10.8
6	9.2	23	8	11.4
7	7.6	21	†	
8	9.4	25	8	11.0
9	9.8	29	7	11.8
10	8.8	29	7	10.8
11	9.8	24	6	10.6
Average	9.1	26	6.9	11.15

Average weekly gain in hemoglobin, 0.27 gm. %.

Group 2.—Medication: Molybdenized Ferrous Sulfate

12	9.4	28	7	13.6
13	9.2	30	8	13.1
14	9.4	27	6	13.7
15	9.0	23	6	13.6
16	9.0	23	6	13.2
17	9.0	25	5	13.4
18	9.4	23	5	13.4
19	9.0	25	6	14.2
20	8.2	28	7	13.4
21	9.0	30	6	13.2
22	7.6	26	6	14.2
Average	8.9	26	6.2	13.5

Average weekly gain in hemoglobin, 0.74 gm. %.

* M.C.H.C.—Mean Corpuscular Hemoglobin Concentration.
† Gastro-intestinal intolerance necessitated discontinuance of ferrous sulfate.

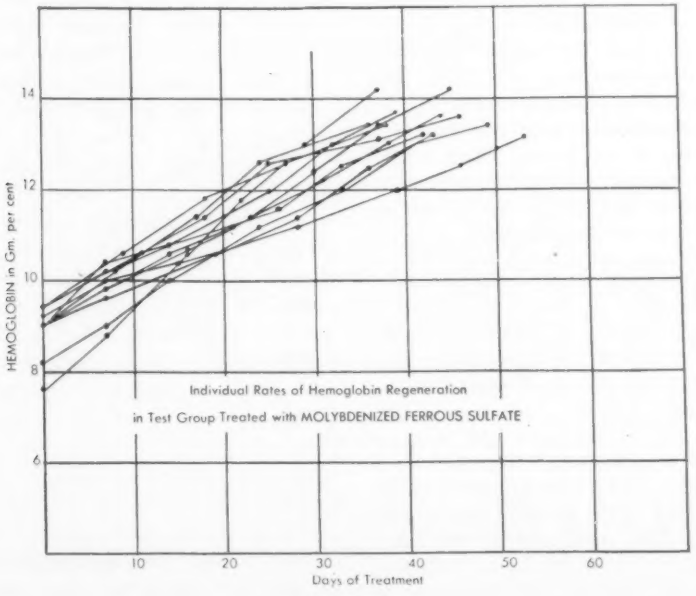

CHART 1

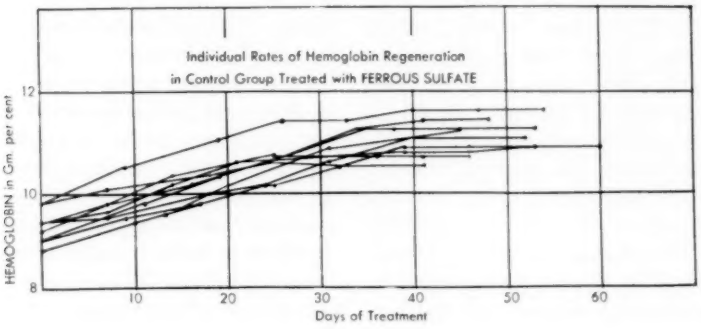

CHART 2

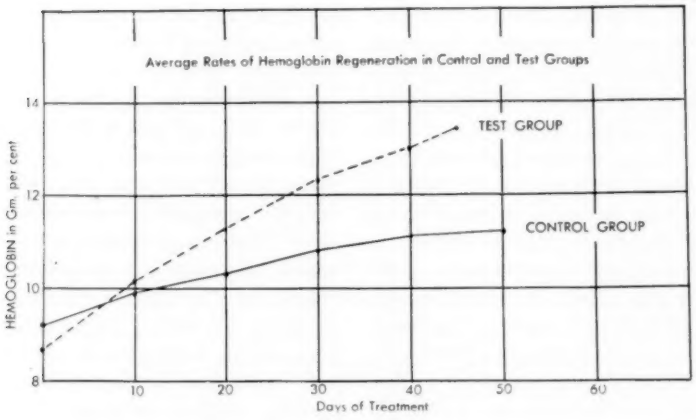

CHART 3

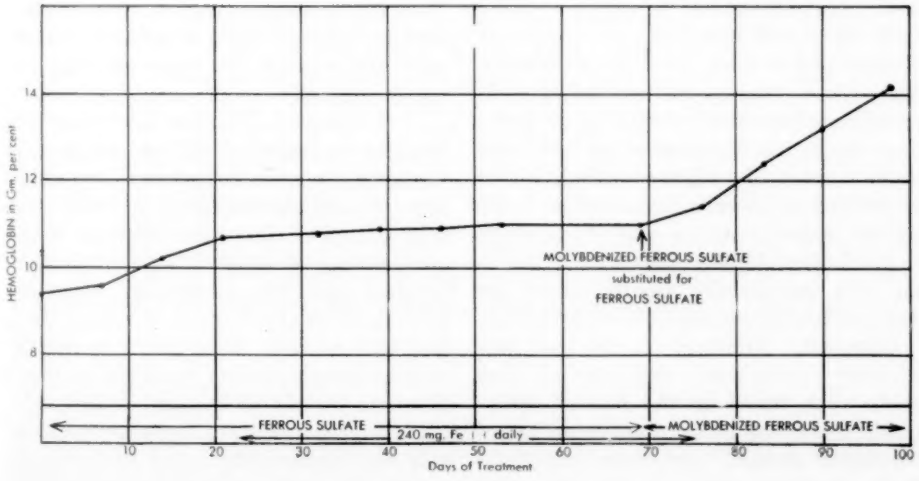

CHART 4

In all but 1 (Case 7) of the patients in Group 1, molybdenized ferrous sulfate was substituted for ferrous sulfate when the curve of therapeutic response had definitely assumed its plateau. Increases in hemoglobin values then occurred in each patient. Moreover, the rate of renewed hemoglobin formation was uniformly rapid until normal values were virtually reached. In Chart 4 is illustrated the renewed therapeutic response in Case 4, which occurred after molybdenized ferrous sulfate had been substituted for ferrous sulfate, and is generally typical of the pattern of renewed response exhibited by the remaining 9 patients similarly treated.

The response of erythrocytes to treatment in both Group 1 and Group 2 generally paralleled the rate of hemoglobin formation. Detailed discussion of the erythrocytic response seems unnecessary, since the rate of hemoglobin increase is the most reliable criterion of the efficacy of treatment in hypochromic anemias.

Gastro-intestinal Tolerance. Gastro-intestinal side effects were not noted in any of the patients during treatment with molybdenized ferrous sulfate. In Group 1, however, it was necessary to discontinue treatment with ferrous sulfate in 1 (Case 7) because of nausea which regularly followed ingestion of the medication. A second patient (Case 11) experienced mild gastro-intestinal irritation during early treatment with ferrous sulfate that disappeared as treatment was continued. Although no conclusions concerning comparative tolerance of the 2 iron preparations are justified because of the relatively small number of patients studied, it was interesting to observe that in Case 7 the patient experienced no side-effects from molybdenized ferrous sulfate with which she was successfully treated after her demonstrated intolerance of ferrous sulfate.

Comment. Arbitrary standards of satisfactory therapeutic response to iron medication, based on the rate of hemoglobin formation in uncomplicated hypochromatic anemia, have been reported.[6] Such standards, however, do not seem applicable in hypochromic anemia of pregnancy. The latter condition is known to impair the response to iron,[14] undoubtedly because one or more factors responsible for the anemia in pregnancy—such as the fetal requirements for blood-building materials—continue to be operative during the period of gestation. Consequently, a dosage of an iron preparation, sufficient to effect an optimal response in uncomplicated hypochromic anemia, might well be less effective in hypochromic anemia during pregnancy.

In the patients of Group 1, hemoglobin values were observed to rise, under treatment with ferrous sulfate, only to subnormal levels of 10.5 to 11.5 gm. %, despite continued treatment with ferrous sulfate in a daily dosage that one would expect to be fully effective in uncomplicated hypochromic anemia. That this subnormal plateau effect is the result of suboptimal dosage of ferrous sulfate was indicated by the renewed therapeutic response which was observed to follow a 50% increase in the daily intake of ferrous sulfate. Similarly, the average rate of hemoglobin formation in Group 1 (0.27 gm. % weekly for the entire therapeutic period), even if calculated for the first part of the therapeutic period during which hemoglobin values actually rose, would approximate only 0.4 gm. % weekly. This response is less than one would anticipate in uncomplicated anemia of comparable degree with the same quantity of ferrous sulfate.

In the patients of Group 2, however, the response to treatment with approximately the same dosage of ferrous iron, but in the form of molybdenized ferrous sulfate, was fully effective. It seems, therefore, that a daily dosage of approximately 240 mg. of bivalent iron was suboptimal, when administered in the form of ferrous sulfate, but was optimal, when given as molybdenized ferrous sulfate, in the 22 patients observed in this preliminary study.

Since recovery from hypochromic anemia was consistently rapid under treatment with molybdenized ferrous sulfate,

as compared with ferrous sulfate, the question of the mode of action of this newer preparation naturally arose. Speculating that the superior therapeutic effect of molybdenized ferrous sulfate might possibly result from an increased absorption of iron, we endeavored to study the comparative degree of gastro-intestinal absorption of this element, when administered as ferrous sulfate and as molybdenized ferrous sulfate, according to the method of Moore and associates.[8,9] The latter investigators have reported that the degree (but not the total amount) of absorption of orally administered iron can be demonstrated through serial measurements of serum iron levels under stated experimental conditions. However, in 4 apparently normal adults we were unable to show by this method any significant difference in degree of iron absorption following oral administration of ferrous sulfate and of molybdenized ferrous sulfate.

In view of the foregoing, therefore, the thought is suggested that the apparently superior therapeutic activity of molybdenized ferrous sulfate in hypochromic anemias may be the result either of an *in vivo* catalysis of iron or, possibly, of a stimulation of erythropoiesis by molybdenum. Piper[10] has reported that molybdenum is an essential element for plant growth. Ter Meulen's[11] finding that molybdenum occurs widely, although in minute amounts, in vegetable and animal materials also suggests the possible rôle of this trace element in animal and human nutrition.

Summary. 1. The hemopoietic activity of a specially processed molybdenized ferrous sulfate, as compared with that of ferrous sulfate, was studied in a series of 22 obstetric out-patients, all having approximately the same degree of true iron-deficiency anemia and all receiving approximately the same daily dose of ferrous iron over the same periods of time.

2. In Group 1, treated with ferrous sulfate, the average gain in hemoglobin was 2.1 gm. % in 6.9 weeks; in Group 2, treated with molybdenized ferrous sulfate, the average gain in hemoglobin was 4.6 gm. % in 6.2 weeks.

3. The pattern of therapeutic response to molybdenized ferrous sulfate seemed to be distinctive, increases in hemoglobin occurring with uniform rapidity until normal values were almost attained; the therapeutic response to ferrous sulfate, although initially satisfactory, became progressively slower until hemoglobin values remained stationary at subnormal levels despite continuation of treatment.

4. The substitution of molybdenized ferrous sulfate for ferrous sulfate, when the latter compound no longer produced increments in subnormal hemoglobin values in Group 1, was followed by satisfactory renewal of hemoglobin formation until normal values were attained. Renewed therapeutic response was also effected by increasing the dosage of ferrous sulfate.

5. Patients treated with molybdenized ferrous sulfate tolerated the preparation extremely well; 1 patient, unable to tolerate ferrous sulfate, was treated effectively and without side-effects by molybdenized ferrous sulfate.

6. Molybdenized ferrous sulfate, therefore, seems to be an unusually efficacious, well-tolerated agent for treatment of true iron-deficiency anemia of pregnancy. Further study of its apparent advantages and its mode of action is in progress.

The assitance of Mrs. Blance M. Brant, who conducted all clinical laboratory tests, is gratefully acknowledged.

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THE EFFECT OF METHYLXANTHINES ON THE PROTHROMBIN TIME AND THE COAGULATION OF THE BLOOD

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In the course of investigations concerning diuresis, Nonnenbruch and Szyszka discovered that in rabbits the coagulability of the blood increased so much after an intravenous injection of a mixture of theophylline and ethylenediamine that it was difficult to obtain blood from the ear vein because of the immediate clotting. This led to studies by these authors[10] and others[1,7] of the effect of theophylline with ethylenediamine on the coagulation of blood in animals and man. The original observations were confirmed and this drug was recommended as a coagulant in cases with hemorrhagic diathesis.[8,10,11] The effect was attributed primarily to the action of the ethylenediamine.[10] Recently, it was shown that the methylxanthines (theophylline, theobromine and caffeine) exert a distinct effect on the prothrombin time and shorten it to a degree which may have clinical importance.[4]

We investigated the effect on prothrombin coagulation time and on plasma coagulation in man produced by the intravenous injection of theophylline and ethylenediamine (aminophylline) and theophylline with sodium acetate and by the oral administration of several methylxanthines.

Method of Study. All subjects were hospitalized on the medical wards. Care was taken to eliminate all patients who had any hepatic disease and those who were receiving vitamin K, salicylates, quinidine or any product which influences the prothrombin concentration or the clotting mechanism. With 2 exceptions all were males because in them venipuncture is much easier and also because they are less apt to object to the repeated venipuncture.

Control (normal) prothrombin and plasma coagulation times were first done. Then, the patients were given 0.5 gm. of aminophylline or theophylline with sodium acetate intravenously; blood was taken 1, 2, 3 and 24 hours after the injection for estimation of the prothrombin and plasma coagulation times. Those who received the methylxanthines by mouth were tested after periods of 24, 48, 72, 96 and 120 hours.

The prothrombin test was done as follows: one-tenth of 1 cc. of a 10% solution of potassium oxalate was placed into a graduated centrifuge tube. A venipuncture was done with as little trauma as possible and blood drawn into an absolutely dry syringe. Enough blood was added to the centrifuge tube to make up 4.5 cc. of the mixture. This was centrifuged at 1500 r.p.m. for 5 minutes and the oxalated plasma pipetted into a small dry test-tube (75 by 10 mm.). The test was done immediately because it is known that prothrombin is very labile and disintegrates on standing.

The Fullerton modification of the Quick method was employed.[5] Two-tenths of 1 cc. of oxalated plasma was pipetted into a test-tube to which was added 0.2 cc. of Russell viper venom.* The tube was placed into a water bath at 37° C. and 0.2 cc. of 1.11% solution of calcium chloride added. The moment the calcium chloride made contact with the solution, a stop-watch was started. The tube was agitated gently and the first appearance of a fibrin-web was taken as the end-point. All tests were performed in duplicate and a mean computed. This method yielded an average control prothrombin time of 20.3 seconds.

The plasma coagulation tests were done in parallel with the prothrombin. A modification of the method first used by Cheney, who in turn had modified the original Howell

* We are indebted to Burroughs Wellcome & Co., for our supply of Stypven, Russell viper venom.

prothrombin concentration test, was employed.[3] These tests were done at laboratory room temperature which varied between 25° and 28° C. Two-tenths of 1 cc. of oxalated plasma (prepared as in the prothrombin time test) was pipetted into a test-tube (75 by 10 mm.) and 0.2 cc. of 1.11% of calcium chloride added. The tube was agitated gently for 10 seconds, to assure thorough mixing, and then tilted to the horizontal every 30 seconds and oftener as coagulation began. When the solution did not flow on tilting the test-tube to the horizontal, this was considered the end-point.

prothrombin time was shortened by more than 3 seconds. In 21 cases, the prothrombin time was determined 1 hour following the injection and in 18 of these a distinct shortening appeared within this time. The most marked shortening was obtained 1 hour after the injection in 8 cases, 2 hours after the injection in 3 cases and in 3 hours after the injection in 9 cases.

Figure 1 shows a graph of those cases that had the greatest decrease in the pro-

TABLE 1.—THE EFFECT OF INTRAVENOUS AMINOPHYLLINE (0.5 GM.) ON THE PROTHROMBIN TIME

			Prothrombin time (sec.)						
				Hours after taking of drug				Maximum	
Name	Age	Sex	Control	1	2	3	24	change	Diagnosis
W. U.	54	M	26.0	16.8	17.4	21.6	19.0	9.2	Peptic ulcer
B. B.	32	M	20.0	20.2	17.0	15.0	17.0	5.0	Peptic ulcer
J. D.	65	M	21.2	20.0	19.0	13.2	18.6	8.0	Brain tumor
D. G.	45	M	21.0	19.0	20.0	15.0	20.0	6.0	Diabetes
A. B.	79	M	22.6	21.4	24.8	15.8	17.8	6.8	Pneumonia
A. B.	79	M	16.0	18.0	14.0	16.4	16.6	2.0	Hypertension
W. G.	36	M	17.2	14.8	15.4	17.0	12.6	4.6	Lues
L. H.	28	M	20.0	13.0	18.7	16.0	18.0	7.0	Pleurisy
B. H.	79	M	17.0	15.8	18.2	17.6	16.8	1.2	Bronchitis
J. A.	50	M	20.8	19.0	19.0	18.8	18.0	2.8	Coronary thrombosis
A. T.	38	M	21.0	23.0	29.0	28.8	35.0	−14.0	Colitis
V. K.	16	M	18.2	20.6	18.0	16.4	20.6	1.8	Pneumonia
J. L.	47	M	22.2	20.0	19.4	19.8	20.2	2.8	Lung tumor
A. R.	37	M	18.6	17.2	15.8	16.6	19.8	2.8	Amebiasis
J. B.	66	M	17.4	15.6	18.2	12.4	20.8	5.0	Bronchiogenic carcinoma
J. U.	25	M	18.8	18.4	17.0	13.0	18.6	5.8	Schistosomiasis
C. J.	73	M	21.2	17.4	16.4	14.0	20.0	6.2	Prostatic hypertrophy
H. G.	49	M	17.2	15.0	15.0	15.2	17.2	2.2	Empyema
A. G.	52	M	19.0	18.0	14.5	14.2	17.0	5.8	Coronary thrombosis
H. T.	14	M	19.0	16.4	16.4	17.5	20.2	4.8	Pneumonia
R. W.	77	F	24.0	18.5	18.5	..	16.8	7.2	Ptosis, right kidney
G. M.	31	F	23.5	..	14.0	..	19.0	9.5	Petit mal

This test is somewhat empiric, as no attempt was made to determine the optimal amount of calcium chloride necessary to give the shortest coagulation time; however, our normal controls had an average of 4.9 minutes and this compares favorably with Cheney's average of 5.2 minutes.

Results. *Intravenous Injection of Aminophylline.* The effect of intravenous aminophylline was investigated in 22 patients. The data on prothrombin time are compiled in Table 1. The ages of the patients varied between 14 and 79 years. Of 22 cases, 21 showed a shortening of the prothrombin times following the injection. The 1 exception concerned a 38 year old male with colitis; he showed a steady increase of 14 seconds in 24 hours. The smallest change was 1.2 seconds and the greatest was 9.5 seconds. In 14 cases, the thrombin time at the end of 3 hours. The results are uniform. In 2 instances, Cases R. W. and G. M., the prothrombin time was determined 6 hours after injection and in both there was a distinct tendency to return to control levels as compared to the value obtained after 3 hours.

The results of the measurements of the plasma coagulation times are compiled in Table 2. The first 20 cases in Table 1 were also used for this investigation. The coagulation time was shortened following the injection of aminophylline in 18 of the 20 cases studied. In 2 cases it remained unchanged after 1 hour and then gradually increased. In 15 cases the shortening of the coagulation time was greater than 1 minute. Even in the case of colitis (A. T.), in which the prothrom-

bin time paradoxically became prolonged, the coagulation time was distinctly shortened. The decrease in clotting time was distinct in 1 hour in 10 cases. In 7 cases it was shortest after 2 hours and in 6 cases at the end of 3 hours. In 3 cases the shortest coagulation time was found 24 hours after the injection. In 24 hours, the coagulation time was distinctly increased in 16 cases and in 12 of these

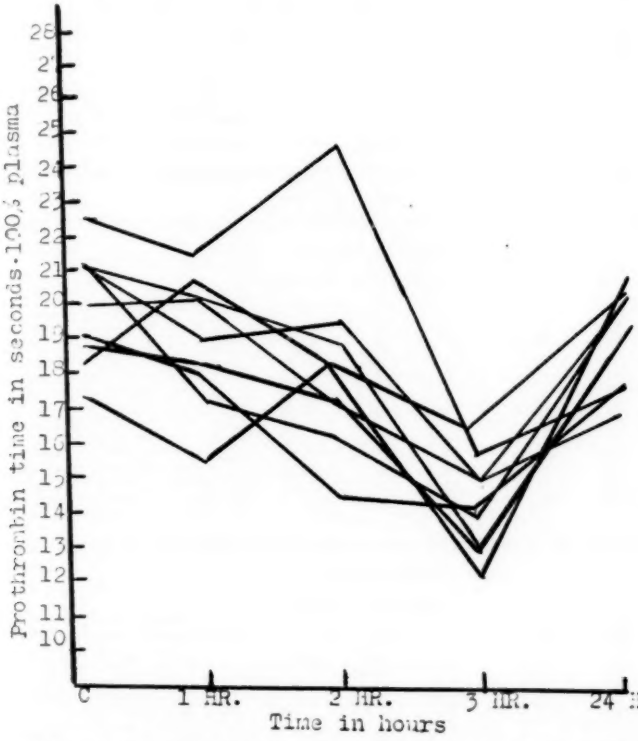

FIG. 1.—Showing all those cases that had a maximum shortening of the prothrombin time in 3 hours (aminophylline, 0.5 gm. intravenously).

TABLE 2.—THE EFFECT OF INTRAVENOUS AMINOPHYLLINE (0.5 GM.) ON PLASMA COAGULATION TIME

			Plasma coagulation time (min.)						
				Hours after taking of drug				Maximum	
Name	Age	Sex	Control	1	2	3	24	change	Diagnosis
W. U.	54	M	2.4	2.5	1.6	2.6	2.0	0.8	Peptic ulcer
B. B.	32	M	2.0	2.0	2.0	2.2	3.8	−1.3	Peptic ulcer
J. D.	65	M	4.0	3.4	3.3	3.6	4.0	0.7	Brain tumor
D. G.	45	M	3.9	5.3	6.9	3.1	3.3	0.8	Diabetes
A. B.	79	M	7.3	4.1	6.0	4.1	3.7	3.6	Pneumonia
A. B.	79	M	3.1	4.0	2.1	2.0	2.2	1.1	Hypertension
W. G.	36	M	3.0	3.3	2.0	2.5	3.0	1.0	Lues
E. H.	28	M	4.9	2.7	2.2	1.9	4.9	3.0	Pleurisy
B. H.	79	M	4.0	4.0	3.6	4.2	2.2	1.8	Bronchitis
J. A.	50	M	6.1	5.6	5.5	5.5	2.5	3.6	Coronary thrombosis
A. T.	38	M	5.2	4.0	3.8	3.0	5.0	2.2	Colitis
A. K.	16	M	3.2	2.0	3.4	3.8	3.4	1.2	Pneumonia
J. L.	47	M	3.3	3.5	2.0	2.7	5.0	1.3	Lung tumor
A. R.	37	M	3.0	3.0	4.0	3.6	3.5	−1.0	Amebiasis
J. B.	66	M	3.8	4.7	2.6	2.3	5.0	1.5	Bronchiogenic carcinoma
J. U.	25	M	5.0	2.3	3.7	3.2	4.0	2.7	Schistosomiasis
C. J.	73	M	5.3	3.0	2.5	2.7	5.3	2.8	Hypertrophy prostate
H. G.	49	M	5.2	5.3	2.0	2.3	7.0	3.2	Empyema
A. G.	52	M	7.0	3.3	4.8	2.5	7.5	4.5	Coronary thrombosis
H. T.	14	M	4.7	2.3	2.0	2.5	6.3	2.7	Pneumonia

the control values were reached or surpassed.

Intravenous Injection of Theophylline With Sodium Acetate. The results on the 12 cases studied are compiled in Tables 3 and 4. Although the ages ranged from 22 to 85 years, 11 of the patients were 50 or more years old. Eleven of the 12 subjects showed a significant shortening of the prothrombin time; the smallest was 0.4 second, as compared with 1.2 seconds for aminophylline, and the greatest shortening was 6.8 seconds as compared with 9.5 seconds for aminophylline. The average decrease in prothrombin time was 4.29 seconds as compared to 4.7 seconds for aminophylline. In 5 of the 12 patients, the greatest hyperprothrombinemic effect of the drug occurred after 24 hours; in 4 in 2 hours; in 2 in the 1st hour; and in 1 at the 3rd hour after injection. This is in contrast to aminophylline where the majority of the patients (14) had returned to their control levels after 24 hours. Seven of the patients had a significant shortening as early as 1 hour. One of the patients (M. J.) who had a pulmonary infarct died from multiple embolic phenomena, before the experiment could be completed. It is interesting to note that although he had a very short control prothrombin time (14 seconds), the hyperprothrombinemia increased during the embolic episode with a shortening of the prothrombin time to 8.4 seconds.

Eight of the 12 subjects showed a shortening of the plasma coagulation. This ranged from 0.8 to 5 minutes. Four of the patients exhibited a lengthening of the coagulation time for which no explanation can be given. Of those who had a decrease in time, the average was 3.03 minutes as compared to 2.1 minutes for aminophylline. The maximum decrease was evenly divided among the 1, 2, 3 and 24 hour periods after injection.

No correlation between the effect on the prothrombin and coagulation times is possible; those cases (C. J., M. J., W. M., A. S.) with a lengthening of the coagulation time showed the most significant shortening of the prothrombin time.

Patients C. J. and J. A. were tested with both aminophylline and theophylline with

TABLE 3.—THE EFFECT OF (I. V.) THEOPHYLLINE SODIUM ACETATE (0.5 GM.) ON PROTHROMBIN TIME

			Prothrombin time (sec.)						
				Hours after taking of drug				Maximum	
Name	Age	Sex	Control	1	2	3	24	change	Diagnosis
A. B.	56	M	22.0	23.2	21.2	21.4	17.4	4.6	Arthritis
A. L.	54	M	19.2	21.6	20.0	20.6	18.8	0.4	Cerebral hemorrhage
C. J.	73	M	22.8	19.8	18.4	21.0	16.8	6.0	Prostatic hypertrophy
M. J.	67	M	14.0	13.2	8.4	16.8	..	5.6	Pulmonary infarct
J. A.	50	M	20.4	18.2	16.0	18.6	14.6	5.8	Coronary thrombosis
E. J.	22	M	18.6	17.0	22.5	21.2	14.8	3.8	Arthritis
J. L.	55	M	20.0	19.6	17.2	19.8	21.2	2.8	Cerebral hemorrhage
W. M.	70	M	22.4	20.8	16.0	18.4	17.4	6.4	Arthritis
J. D.	85	M	20.6	17.8	15.6	17.2	21.6	5.0	Coronary sclerosis
J. R.	35	M	22.0	15.2	16.2	18.0	22.0	6.8	Bleeding, peptic ulcer
S. P.	68	M	22.0	19.6	22.0	20.4	21.2	2.4	Hemiplegia
A. S.	63	M	20.8	22.0	21.6	19.0	22.6	1.8	Parkinson's disease

TABLE 4.—THE EFFECT OF (I. V.) THEOPHYLLINE SODIUM ACETATE (0.5 GM.) ON COAGULATION TIME

			Coagulation time (min.)						
				Hours after taking of drug				Maximum	
Name	Age	Sex	Control	1	2	3	24	change	Diagnosis
A. B.	56	M	8.0	8.3	9.0	8.0	..	11 −1	Arthritis
A. L.	54	M	6.3	7.3	5.5	6.0	..	0.8	Cerebral hemorrhage
C. J.	73	M	6.0	7.0	11.5	7.0	..	−5.5	Prostatic hypertrophy
M. J.	67	M	2.5	2.8	3.0	3.7	..	−1.2	Pulmonary infarct
J. A.	50	M	5.0	5.8	4.0	6.0	2.3	2.7	Coronary thrombosis
E. J.	22	M	4.5	4.0	6.5	5.0	1.5	3.0	Arthritis
J. L.	55	M	8.5	7.0	8.5	3.5	6.5	5.0	Cerebral hemorrhage
W. M.	70	M	3.5	9.0	9.0	3.5	4.0	−5.5	Arthritis
J. D.	85	M	8.0	7.0	7.5	3.5	10.5	4.5	Coronary sclerosis
J. R.	35	M	6.5	4.5	3.0	3.3	5.5	3.5	Bleeding, peptic ulcer
S. P.	68	M	5.5	3.3	5.0	4.7	9.0	2.2	Hemiplegia
A. S.	63	M	6.0	3.5	6.5	7.5	7.5	2.5	Parkinson's disease

sodium acetate. The former showed a decreased prothrombin time of 6.2 seconds with aminophylline and 6 seconds with theophylline with sodium acetate and the latter a shortening of 2.8 seconds with aminophylline and 5.8 seconds with theophylline with sodium acetate. C. J. showed a lessened coagulation time of 2.8 minutes with aminophylline and an increased time of 1 to 5.5 minutes with theophylline with sodium acetate, while showed a significant shortening in the prothrombin time which averaged 4.65 seconds as compared to intravenous aminophylline with 4.7 seconds, and intravenous theophylline with sodium acetate with 4.29 seconds. Six of the subjects were tested 24 hours after ingestion of the drug, and 3 showed a detectable hyperprothrombinemia. In 1 case (N. P.), the maximum shortening occurred in the 24 hour period. Patients H. G. and A. G.

TABLE 5.—THE EFFECT OF THE METHYLXANTHINES (BY MOUTH) ON PROTHROMBIN TIME

				Prothrombin time (sec.)							
					Hours after taking of drug						
Name	Age	Methyl-xanthines	Dose (gm. t.i.d.)	Control	24	48	72	96	120	Maximum change	Diagnosis
H. G.	49	Theobromine	1.0	20.0	..	..	15.3	..	..	4.7	Empyema
A. G.	52	Theobromine	1.0	21.0	..	..	14.5	..	..	6.5	Coron. thrombosis
T. H.	73	Aminophyllin	0.5	22.3	..	..	20.5	16.5	..	5.8	Arteriosclerosis
J. C.	80	Aminophyllin	0.5	24.5	..	..	24.8	18.4	..	6.1	Arteriosclerosis
A. S.	53	Aminophyllin	0.5	21.6	..	..	22.4	22.0	..	−0.8	Neurosyphilis
L. B.	47	Theobromine	1.0	20.6	..	14.6	..	..	..	6.0	Beri-beri, heart
J. C.	41	Theobromine	1.0	18.2	19.6	19.8	15.7	20.4	..	2.5	Virus pneumonia
J. Y.	59	Theobromine	1.0	21.4	19.2	19.8	18.4	16.4	..	5.0	Coronary sclerosis
N. P.	57	Theobromine	1.0	20.2	14.9	18.4	17.5	19.0	..	5.3	Abdominal mass
I. K.	48	Theobromine Sodium acetate	0.5	18.0	..	..	..	..	15.4	2.6	Hypertension
S. S.	31	Theobromine Sodium acetate	0.5	18.2	..	..	..	..	19.0	−0.8	Coron. thrombosis
T. Q.	57	Theobromine	1.0	19.0	20.0	19.8	23.0	..	..	−4.0	Mitral stenosis
U. M.	62	Theobromine	1.0	16.2	18.4	16.8	18.4	..	..	−2.2	Gastric carcinoma
M. D.	73	Theobromine	1.0	19.4	18.0	17.4	20.2	..	..	2.0	Hemiplegia

TABLE 6.—THE EFFECT OF THE METHYLXANTHINES (BY MOUTH) ON PLASMA COAGULATION TIME

				Coagulation time (min.)							
					Hours after taking of drug						
Name	Age	Methyl-xanthines	Dose (gm. t.i.d.)	Control	24	48	72	96	120	Maximum change	Diagnosis
H. G.	49	Theobromine	1.0	7.0	..	..	6.0	..	..	1.0	Empyema
A. G.	52	Theobromine	1.0	6.3	..	..	5.5	..	..	0.8	Coron. thrombosis
T. H.	73	Aminophyllin	0.5	5.0	..	..	7.0	7.0	..	−2.0	Arteriosclerosis
J. C.	80	Aminophyllin	0.5	4.0	..	..	8.5	7.4	..	−4.5	Arteriosclerosis
A. S.	53	Aminophyllin	0.5	3.5	..	..	9.0	8.0	..	−5.5	Neurosyphilis
L. B.	47	Theobromine	1.0	7.0	..	4.0	..	..	..	3.0	Beri-beri, heart
J. C.	41	Theobromine	1.0	5.8	7.0	7.5	6.0	5.7	..	−1.7	Virus pneumonia
J. Y.	59	Theobromine	1.0	5.5	5.3	6.5	5.5	6.5	..	0.2 −1	Coron. sclerosis
N. P.	57	Theobromine	1.0	4.0	2.5	5.0	7.5	6.0	..	1.5	Abdominal mass
L. K.	48	Theobromine Sodio-acetate	0.5	4.0	..	..	..	..	3.5	0.5	Hypertension
S. S.	31	Theobromine Sodio-acetate	0.5	3.0	..	..	..	..	6.3	−2.7	Coron. thrombosis
T. Q.	57	Theobromine	1.0	7.5	6.0	3.0	7.0	..	..	4.5	Mitral stenosis
U. M.	62	Theobromine	1.0	3.5	4.0	6.3	7.0	..	..	−3.5	Gastric carcinoma
M. D.	73	Theobromine	1.0	7.5	2.0	3.0	5.5	..	..	5.5	Hemiplegia

J. A. had a decreased time of 2.5 minutes with the former drug and a shortened time of 2.7 minutes with the latter medication.

Effect of Methylxanthines by Mouth. This study was done on 14 patients who received the methylxanthines in the form of capsules of theobromine, 1 gm. 3 times daily, tablets of aminophylline, 0.5 gm., 3 times daily, and enteric-coated tablets of theobromine sodium acetate, 0.5 gm., 3 times daily. The results are summarized in Tables 5 and 6. Ten of the 14 patients received theobromine 1 gm., 3 times daily, and were tested 72 hours later. They had also been previously tested with intravenous aminophylline. The patient, H. G., had a lessening of the prothrombin time of 2.2 seconds following the intravenous administration of aminophylline as compared with 4.7 seconds after the oral medication. The patient, A. G., showed a decrease of 5.8 seconds with intravenous aminophylline as compared with 6.5 seconds for theobromine by

mouth. Three patients were studied on 4 consecutive days; 1 showed a maximum reduction on the 3rd day, 1 on the 4th and 1 on the 1st day. In 4 patients the prolongation of the prothrombin time varied from 0.8 to 4 seconds. This lengthening occurred with all 3 of the drugs used.

A study of Table 5 indicates that all 3 drugs were equally effective in reducing the prothrombin time, and that this reduction equals that produced by the intravenous methylxanthines.

Seven of the 14 patients developed a shortened coagulation time ranging from 0.5 to 5.5 minutes. The other 7 had a lengthened coagulation time of 1 to 5.5 minutes. Again, no parallelism between the prothrombin and clotting times can be drawn for those who had a decrease in the prothrombin time showed an increased coagulation time; the reverse was also true. In 3 instances (U. M., S. S., and A. S.) prolongation of both the prothrombin and clotting times occurred after the oral administration of methylxanthines.

Discussion. The investigations reported above show a definite shortening of the prothrombin time and of the plasma coagulation time following an intravenous injection of aminophylline. The changes were often found within 1 hour after the injection and they seem to reach a maximum 4 to 5 hours later. Often the values were still abnormal after 24 hours. A cumulative effect of injections administered daily for some time is therefore possible.

The intravenous injection of theophylline with sodium acetate had a similar effect. Therefore the action is not bound to the ethylenediamine[10] which is used as a solvent for the theophylline.

The increased coagulability of the blood following the administration of aminophylline led to the recommendation of this drug as a styptic agent.

Aminophylline and other methylxanthines are, however, widely employed for their diuretic effect in bedridden cardiac patients. The danger of thrombosis in the veins of the lower extremities of such patients is great, since anatomic evidence shows that it occurs in more than 50% of all autopsies in a general hospital.[6,9] Aminophylline is also used frequently in patients with coronary sclerosis who may at any time develop a coronary thrombosis. It is often given for Cheyne-Stokes respiration, where it has a specific effect. It is administered in cardiac asthma and is given to dilate the coronary arteries.[2] It is not probable that the changes in the prothrombin time *per se* will have a detrimental effect in a patient with a normal circulation who is not confined to bed. The possibility, however, that the increased coagulability of the blood will augment the danger of venous thrombosis in the bedridden patient or the risk of coronary thrombosis in a patient with coronary sclerosis merits serious consideration.

During the last 20 years we have given aminophylline and theophylline with sodium acetate intravenously to a large number of patients. Occasionally coronary thrombosis appeared during the treatment but this was considered to be an accidental event. Perhaps now that attention has been directed to a possible causal relationship between such an accident and the administration of methylxanthines more observations will be available of such accidents.

Perhaps the administration of dicoumarin will be necessary in those patients in whom the methylxanthines are indicated.[4]

The cause of the hyperprothrobinemia following the administration of methylxanthines is unknown. A functional stimulation of the hepatic tissue has been suggested as a causative factor.[4]

Summary and Conclusions. Shortening of the prothrombin time and of the plasma coagulation time was observed in man following the intravenous administration of aminophylline and theophylline with sodium acetate. Methylxanthines, given orally have a similar effect.

The clinical implications of these findings are discussed.

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BLOOD LEVELS OF PENICILLIN AFTER VARIOUS FORMS OF ORAL ADMINISTRATION

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The destructive action of the acid of gastric juice[1] is the chief factor opposing effective administration of penicillin by mouth. Many methods are applicable in part in overcoming this factor.

We have investigated the following methods during the past year:

A. The administration of penicillin on an empty stomach when gastric emptying will be rapid and acidity low.

B. The use of various alkalies to bring the pH of the stomach contents up toward the 5 to 7 range where penicillin is most stable. We have confirmed the work of György *et al.*[5] and Charney *et al.*[2] in this respect.

C. The use of a substance that will hold penicillin in a suspension or solution that does not mix readily with the gastric contents and that will thus protect it from the acid and serve to slow the absorption. Libby *et al.*[7] found that cotton-seed oil served this purpose to some extent. We have found a mixture of lanolin and sesame oil[7] and also cocoa butter to be suitable.

D. The use of an enteric coated capsule that will carry penicillin to the small intestine before disintegrating. The ideal coating would be one completely insoluble in acid and readily soluble in alkali. Of various coatings tried, we have found a resin[11] most satisfactory.

E. The use of an adsorbing agent that would release penicillin slowly.

F. Combinations of the above methods.

Procedure. Blood penicillin levels have been determined by the Fleming slide cell method[4] and urine concentrations by the Oxford cup method.[1]

One group of subjects were given the drug in aqueous solution without any accompanying medication. Part of these subjects (Table 1) received the drug on an empty stomach and part received the drug after a meal. It is obvious that the presence of food greatly increases the destruction of penicillin. When the drug was taken with a meal, no measurable amount was present in the blood at the end of 2 hours and only approximately 1% was excreted in the urine. When taken on an empty stomach, the amount excreted varied from 6.6 to 15.9%. On 1 experiment, it was noted that penicillin appeared in the urine 3 minutes after oral medication.

Table 1.—Blood Levels of Penicillin After the Oral Administration of 100,000 Units of Calcium Penicillin in Tap Water

Subject	Blood levels (Oxford units per cc. of blood) ½ hr.	1 hr.	1½ hrs.	2 hrs.	3 hrs.	4 hrs.	% excretion
S*	..	0.06	0.03	0	0	..	6.6
S*	..	0.12	..	0.03	0		
W*	0.12	0.12	0	0.06	0	..	15.9
S†	0	0	0	0	..	..	1.9
W†	..	0	0	0	0	..	1.5
S†	..	0.12	0	0	0	..	1.2
W†	0.03	0	0	0	0	..	0.48
R‡	..	0.24	..	..	0.24	0.03	24.2

* Empty stomach. † Full stomach. ‡ Pernicious anemia.

One group of subjects (Table 2) was given the drug dissolved in a saponified lanolin-

sesame oil base.[8] Capsules were given containing 10,000 to 20,000 units in 0.5 to 1 gm. of the base. The subjects were allowed to have liquids only. An initial dose of 200,000 units was given followed by a second dose in 4 or 5 hours as indicated in the table. Blood samples were taken at hourly intervals for 8 hours and urine samples were collected for 12 to 24 hours. As indicated in the table, blood levels of 0.015 unit per cc. or above were maintained over an 8 hour period. The amount excreted in the urine varied from 3 to 20%.

A third group of subjects (Table 3) received the drug suspended in cocoa butter and placed in enteric coated capsules. A dose of 100,000 units was given initially and repeated at the end of 3 hours. Blood samples were taken at hourly intervals for 3 hours and, in 3 subjects, at the 6th hour. In 8 of the 10 subjects, blood levels ranging from 0.03 to 0.12 unit per cc. were still present at the end of 3 hours. In the subjects of this group in which satisfactory urine studies were made, the percentage of excretion varied from 3 to 21%. As compared with the results of the first 3 hours with the lanolin-sesame emulsion, it is apparent that the enteric coating facilitated higher blood levels with half the penicillin dosage.

A fourth group of subjects (Table 4) was

TABLE 2.—BLOOD LEVELS OF PENICILLIN AFTER ORAL ADMINISTRATION OF 200,000 UNITS IN SAPONIFIED LANOLIN AND SESAME OIL EVERY 5 HOURS

	Blood levels (Oxford units per cc. of blood)							
Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	7 hrs.	8 hrs.
1. Ha.	0.03	0.03	0.03	0.03	0	..	..	0.015
2. Ga.	0.015	0.015	0.015	0.015	0	0.03	0.06	0.06
3. Di.	0.03	0.06	0.03	0.015	0.015	0.015	0.03	0.03
4. Ma.	0.24	0.12	0.03	0.03	0.03	0.12	0.06	0.015
5. Ma.	..	0.06	..	0.12	..	0.12	..	0.015
6. Hal.	0.03	0.06	0.015	0.015	0.015	0.015	0.03	
7. Sm.	0.03	0.03	0.015	0.03	..	..	0.03	
8. Hi.	0.12	0.12	0.12	0.06				
Average	0.07	0.062	0.036	0.038	0.015	0.06	0.042	0.05

TABLE 3.—BLOOD LEVELS OF PENICILLIN AFTER ORAL ADMINISTRATION OF 100,000 UNITS IN ENTERIC COATED CAPSULES EVERY 3 HOURS

	Blood levels (Oxford units per cc. of blood)			
Subject	1 hr.	2 hrs.	3 hrs.	6 hrs.
1	0.06	0.12	0.12	0.06
2	0.24	0.24	0.12	0.06
3	0.48	0.12	0.06	0.48
4	0.24	0.12	0.06	
5	..	..	0.12	
6	0	0.06	0	
7	0	0	0	
8	0.24	0.06	0.03	
9	0.48	0.24	0.06	
10	0.48	0.48	0.12	
Average	0.24	0.16	0.069	

TABLE 4.—BLOOD LEVELS OF PENICILLIN AFTER ORAL ADMINISTRATION WITH 100,000 UNITS OF CALCIUM PENICILLIN IN ALUMINUM HYDROXIDE GEL

	Blood levels (Oxford units per cc. of blood)			
Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
K	0	0.06	0.015	0.015
L	0.03	0.015	0.015	0
R	0.12	0.06	..	0
F	0.12	0.03	0.03	0
W	0.24	0.12	0.015	
G	0.03	0.03	0.03	0.03
St	0.24	0.24	0.06	0
Average	0.11	0.079	0.03	0.007

given 100,000 units of the drug with 20 cc. aluminum hydroxide gel. Blood levels were followed for 4 hours and urine concentration for 6 to 8 hours. Subjects were given a soft diet low in protein and fat. As compared to the controls it is apparent that the amount of penicillin absorbed is greatly enhanced. Two subjects were given 25,000 units of penicillin in aluminum hydroxide gel prepared according to the method of Welch.[10] This dosage was repeated every 2 hours for 4 doses. Blood and urine samples were taken at hourly intervals for 7 hours and urine collections were continued at intervals for 24 hours. No blood levels of penicillin were demonstrable by our method at any time and only traces appeared in the urine after the 9th hour.

Activated charcoal was found to remove over 99% of penicillin activity, and all but traces of the color and taste of an aqueous solution that was passed through it. On taking 3 gm. of the charcoal containing 99,000+ units of penicillin by mouth in gelatin capsules, however, no measurable amount was found in the blood and only traces appeared in the urine. It was concluded that either charcoal did not prevent destruction by acid or held the penicillin too firmly to allow absorption. To test this hypothesis, 100,000 units were passed through charcoal and assay of the filtrate showed that 99,730 units had been adsorbed. The charcoal was taken in gelatin capsules along with 20 cc. aluminum hydroxide gel. Again no measurable blood levels of penicillin were found and only traces appeared in the urine.

Discussion. It is apparent that various methods may be employed to protect penicillin from destruction by the acid of the gastric juice. The results from the experiments described indicate that the use of alkali or the use of an enteric coating plus a suspending medium give the most satisfactory protection. Gastric acidity and gastric emptying are variable factors even in the same individual. A suitable antacid should be one which can be given in adequate amounts to neutralize the maximum amount of acid expected without at the same time producing a highly alkaline reaction in those with normally low acidity. Other desirable features are the ability to adsorb penicillin and the property of forming an adherent coating to the stomach and intestinal walls. A comparison of the efficiency of various antacids is being conducted.

Preliminary trials with some of the commonly used enteric coatings, especially phenyl salicylate, keratin and stearic acid, showed them to be unsatisfactory. In regard to phenyl salicylate as an enteric coating, it is well to keep in mind the admonition of Sollman[8] that "a coating sufficiently heavy to be effective introduces large doses of salol." Examination of capsules coated by routine methods in a pharmacy revealed them to contain 0.5 gm. or more each. The maximum dose recommended is 2 gm. Fatal cases from phenyl salicylate administration[3] add weight to Sollman's admonition. The use of an enteric coating that depends primarily on a time factor is undesirable because of the variable emptying time of the stomach and activity of the small intestine. The resin coating employed in the experiments disintegrated gradually in an acid medium, but slightly more rapidly in an alkaline medium. The time factor is apparently the dominant one with this coating.

The apparently firm adsorption of penicillin by activated charcoal makes this combination useless for oral administration. This observation is in agreement with the result of Henry and Henry[6] who found that penicillin inhibits the adsorption of methylene blue by activated charcoal.

Summary. Penicillin has been given by the oral route with a number of vehicles. When given on an empty stomach in tap water, blood levels and urinary excretions are considerably greater than when the drug is given after a meal. Penicillin, when given in solution in saponified lanolin and sesame oil, shows enhanced and prolonged blood levels and increased urin-

ary excretion of the drug as compared to the controls with tap water.

The use of an enteric coating in addition to a suspending medium more than doubled the efficiency of absorption of penicillin as compared to a suspending media alone.

The use of aluminum hydroxide along with penicillin gave blood levels of penicillin less than those obtained with an enteric coating. No confirmation was found of the prolonged blood levels of penicillin reported for its use after adsorption by aluminum hydroxide gel.

Penicillin is too firmly adsorbed by activated charcoal to make this combination of value for oral administration.

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UNDER THE CHARGE OF
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INFECTIOUS HEPATITIS

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THE disease entity or entities included under the term *infectious (non-spirochetal) hepatitis* are apparently caused by a filterable virus or group of such viruses which as yet have not been typed for identifying characteristics. The disease is characterized by non-suppurative hepatitis and a systemic response. Jaundice is usually an outstanding feature. In times of war epidemics may be extensive but generally the disease is sporadic. The incubation period approximates 3 to 4 weeks but under certain circumstances may be much longer.[23] The icteric phase of the disease runs a variable course of 3 to 6 or 7 weeks and is followed by complete clinical resolution after a somewhat prolonged convalescence. The term infectious (non-spirochetal) hepatitis does not include all types of infectious hepatitis not due to leptospiral organisms. Amebic hepatitis, yellow fever, and general infections, including syphilis, pneumococcic infection, malaria, tuberculosis, infectious mononucleosis, streptococcal disease and Oroya fever, are excluded, as are the clinical pictures resulting from hepatotoxic chemicals.

Many terms have been used to describe this disease. Sporadic cases have been called *catarrhal jaundice*, a term which very likely has included hepatic degeneration from toxic chemicals when the latter are unknown and probably other types of disease as well. Epidemics have been traced to sporadic cases and the pictures cannot be distinguished. Even though some[62] may still feel they are separate diseases, the problem cannot be settled until etiologic factors are settled. The term *catarrhal jaundice* developed with Virchow's idea that a catarrhal inflammation of the bile ducts was responsible for the picture. As late as in World War I the idea was still prevalent, and Hurst[26] believed that catarrhal jaundice and infectious hepatitis were different diseases. Other terms used include *infectious hepatitis, infective hepatitis, epidemic catarrhal jaundice, common infective hepatic jaundice, non-spirochetal infectious jaundice, campaign jaundice, camp jaundice,* or the equivalents in other languages, as *ictère contagieux, jaunesse de champs,* or *Kriegsicterus.*

ETIOLOGY. Recent work indicates that a filterable virus or group of viruses is responsible for the clinical picture. Characteristics suitable for classifying the agent are lacking. For many years the possibility of a living agent as the cause had been suspected, chiefly because of epidemic occurrence with seasonal peaks in

the autumn and early winter, the rather constant incubation period, and the clinical course. Epidemics have been prone to appear in troop concentrations at such times as in the Napoleonic Wars, the American Civil War, the Spanish American War and both World Wars. In the recent war, numerically it proved to be one of the most important diseases affecting our armies. In the central Mediterranean area the disease reached great epidemic proportions. The importance of the disease in the armed forces has stimulated a great number of investigations which have clarified some of the factors in etiology. Voegt[61] appears to have been the first to transmit the disease to volunteers by the oral administration of duodenal juices and urine. Findlay and Willcox[14] have caused typical icteric and subicteric cases to develop after oral ingestion of feces or of urine from spontaneous cases. Feces filtered through a Seitz filter proved infective in 1 experiment. Such experiments as these, as well as others with transmission through the subcutaneous and intravenous routes establish tentatively that a filterable virus is the probable cause. Blood and stools from patients with infectious hepatitis, taken especially in the pre-icteric stage and up to 2 days after appearance of jaundice, are most uniformly infective.[22] As stated, the duodenal juice is infective in the same stages of the disease. The active agent besides being filterable will withstand 56° C. for ½ hour. It has not yet been identified by the electron microscope.

The natural means of transmission are not clear. The enteric route has long been under strong suspicion. In the Scandinavian countries epidemics have been found in pigs, and in patients an increased incidence was found in the rural areas.[2] Jaundice developed in pigs fed liver from jaundiced pigs and bile from human cases. In general, attempts to transmit the disease to animals have failed. MacCallum and Miles[34] have produced in rats on a protein deficient diet a liver disease by inoculating the blood and feces from patients with infectious hepatitis but English observers have been unable to confirm transmission to pigs. Blumer[7] in this country has noted jaundice following ingestion of pork. Excretion of the virus in the feces and the transmission experiments already cited with feeding of infected feces and duodenal juices strongly favor the oral route of spread. In 1 report of an epidemic in a camp (Neefe *et al.*[40]) the agent was found in well water and was probably the same as that excreted in the feces of the camp patients. Swedish reports[18] also indicate that the disease may be water-borne. Recently Murphy and associates[38] have presented epidemiologic evidence that the disease may be transmitted by milk. In an outbreak of 10 cases in Georgia the evidence, though circumstantial in character, pointed to a single milk supply as the source. Read and her associates[50] in Cleveland studied an outbreak in a medical fraternity and found affected primarily those who ate regularly at the fraternity dining table. The cases were not traceable to previous cases.

The above evidence does not exclude other possible routes of transmission. Droplet infection has figured prominently in suggestions of natural spread. It is not clearly established but is thought by some to be a likely mode of transmission. The disease has been transmitted to volunteers[33] with a nasal spray of nasopharyngeal washings from subjects with the disease in the pre-icteric stage or within 24 hours after developing jaundice. In some such studies infection has occurred in 30 to 50 days.[12] Thus natural infection very likely occurs either by droplet infection through the upper respiratory tract or by food through the gastro-intestinal tract.

Mention must be made here of the clinical entity called *homologous serum jaundice*. This picture at times follows the injection of blood or its products, usually in 6 weeks to 6 months. It has occurred following whole blood transfusion, dried, frozen, or

fresh plasma and serum. It is the type seen in subjects following inoculation with certain batches (icterogenic batches) of yellow fever vaccine containing human serum. This symptom complex is not yellow fever.[56] There is a difference in symptoms and furthermore the virus of yellow fever has not been isolated from these patients. The immune titer for yellow fever is constant as it is in those without jaundice. Also patients already immune to yellow fever have developed homologous serum jaundice and in some of those in whom immunity to yellow fever has not developed because of defective vaccine the picture has appeared. Additional evidence rests in the development of the symptom complex after use of human serum without yellow fever vaccine, especially after the use of measles and mumps convalescent serum. It has also been noted in diabetic and venereal disease clinics in which syringes, contaminated with serum of a previous patient, have been used on other patients without heat sterilization. With contaminated plasma as little as 0.01 cc. has been known to produce the disease. Thus, as well as in contaminated syringes with small amounts of serum, pooled plasma in which someone's serum containing the agent has been added, though highly diluted by the other sera, can produce the disease. In casualties returned to the United States in the past war the frequency of the picture has been as high as 2 to 3%.

The question immediately arises whether homologous serum jaundice is identical with infectious hepatitis, or whether it is a separate disease process. This will not be settled until the causative agent or agents of each are more clearly identified. The clinical manifestations are strikingly the same, but cross-immunization apparently does not occur. Patients are known[20a] to develop infectious hepatitis after having had postvaccinal hepatitis (yellow fever vaccine) a year before. Studies by Neefe, Stokes and Gellis[42] indicate that volunteers recovered from homologous serum jaundice and then inoculated with material known to contain a causative agent of infectious hepatitis developed hepatitis; controls, including reinoculations with material of homologous serum jaundice, were negative. Havens[20b] has obtained similar results. The modes of transmission are, of course, different. Also homologous serum jaundice is seldom connected with secondary cases, unlike infectious hepatitis. The most striking difference in the 2 groups is the extremely long incubation period of homologous serum jaundice. In yellow fever vaccine cases the period has been 9 to 23 weeks (Turner *et al.*[59]). In contaminated syringe cases[53] this period has averaged about 3 to 4 months (Marshall[35]). Experimentally induced attacks produced by inoculations of the original dried pooled human serum from a blood bank which had been used in an icterogenic lot of yellow fever vaccine have shown incubation periods between 59 and 129 days (MacCallum and Bauer[32]). Serum from volunteers who have developed the short incubation form after oral administration produces the short incubation form in other volunteers, whether given orally or parenterally. The agent has survived a temperature of 56° C. for 1 hour and storage in a dry state at 0° C. for many months as well as in a liquid state for a considerable time. The same characteristics hold for the agents of infectious hepatitis.

The difference between the incubation period of naturally occurring infectious hepatitis (about 4 weeks) and that of homologous serum jaundice (3 to 4 months) has been a strong argument that these disease states are separate entities. The lack of facility in experimental transmission by oral administration of feces of homologous serum jaundice,[43] as compared to the ease of transmission of infectious hepatitis, is another point against their unity. Another point which suggests a difference is the failure of homologous serum jaundice to spread from patient to patient and the frequent spread in infectious hepatitis. In 1 study (Neefe *et al.*[44]), injection of homologous serum

products into volunteers showed incubation periods from inoculation to the first appearance of jaundice of from 73 to 110 days although first manifestations of hepatitis were noted within 12 to 50 days in 7 subjects and in from 12 to 35 days in 6 of these. Jaundice appeared late in the hepatic picture. This short incubation period directly concerns the relationship of the disease to infectious hepatitis. Possibly immune bodies in the serum could lengthen the incubation period by temporary protection. Treatment of water contaminated with an agent producing infectious hepatitis is known to have resulted in a decrease in the concentration and possibly the virulence of the agent, so that some modification of the disease may be produced. Evidence suggests that such changes in virulence or concentration may be associated with a prolongation of the incubation period (Neefe *et al.*[41]).

In general then, from the above remarks, it can be seen that the chief differences in the 2 pictures rest in the incubation periods, and epidemiology, the routes of infection, immunity experiments, and, to some degree, in the severity of the clinical picture and mortality figures.

Parenthetically, it may be stated here that certain instances of so-called post-arsphenamine jaundice are not toxic arsenical reactions but homologous serum jaundice. Clinical pictures are indistinguishable and liver biopsies have shown identical changes. As already stated, transmission of the disease has occurred in venereal disease clinics in which syringes have been sterilized by washing with water and alcohol rather than by heat. Bigger[5] has shown that staphylococci mixed with blood drawn into a syringe are not completely removed or killed by this technic. The agent, not destroyed by this means of sterilization, may be injected into the next individual upon whom the syringe is used.[31] In addition there is suggestive evidence (Findlay and Willcox[14]) that concurrent injections of arsenicals may increase the liability to the disease. The same type of transmission has been reported in a diabetic clinic.[10]

Pathologic Anatomy. The pathologic picture of infectious hepatitis was long misunderstood, primarily because of the paucity of postmortem material. In 1855 Bamberger suggested that swelling of the ostium of the common bile duct produced jaundice through obstruction. In 1865 Virchow described a case in which the ostium of the common bile duct was plugged with mucus and he coined the term *catarrhal jaundice*. The traditional concept that a catarrh of the duodenum involved the ampulla of Vater with a mucus plug was supported by clinical evidences of nausea, dyspepsia and other gastro-intestinal symptoms and was not controverted by autopsies, which were infrequent. Many years later Van Rooyen and Gordon[60] carried out intubation studies and showed there is no evidence of duodeno-biliary catarrh. According to Lichtman,[28a] A. Stokes' view, that mechanical obstruction was not the basis of the picture, was first postulated by him in 1839, long before Virchow's prestige established his views, which in turn were supported by reports of a small number of cases with inflammation of the bile ducts. It was not until the period of World War I that hepatitis was generally conceded to be the cause of the picture. At that time Eppinger[11] found, in the livers of soldiers with this disease who had died as the result of trauma, hepatitis without obstruction. Similarly in the Gallipoli campaign necrosis of parenchymatous cells was found under the same conditions. Still later,[9,51] biopsy in various stages of the disease showed a picture characterized by acute necrosis and autolysis, beginning at the center of the lobules, disorganization of the liver cell columns, and leukocytic and especially histiocytic infiltrations into the portal zones. At this time the widespread damage of the liver is so extensive that one wonders how recovery takes place. Reticular framework is not lost and rapid recovery usually ensues. Patients erroneously operat-

ed upon show in their livers swelling with tissues stained green by bile pigments. Biopsies reveal cloudy swelling. With recovery the picture returns to normal. Recent studies (Lucké[30b]) of patients who died of accidents at variable intervals after infectious hepatitis have confirmed these views by proving healing with only slight residual traces of liver injury not indicative of persistent or progressive damage.

Severe attacks of infectious hepatitis leading to death have supplied material for pathologic study. In the liver the picture resembles that of acute yellow atrophy. This form of yellow atrophy differs from that caused by hepatotoxic chemicals (Lucké[30a]).

Recent studies of livers in homologous serum jaundice have shown similar pictures with necrosis, atrophy, and varying degrees of regeneration. Councilman bodies, as found in yellow fever, have also been noted (Hayman[24]).

Lesions in organs other than the liver also occur in infectious hepatitis. The spleen is enlarged in the majority of instances due to cellular proliferation and, in later stages, to congestion. Lymphadenopathy appears. The kidneys may show the characteristics of the lower nephron syndrome, a cholemic nephrosis. In late stages hemorrhages are common, especially in the lungs and gastro-intestinal tract as well as in other tissues such as the heart, mediastinum and pleura. Electrocardiographic changes have been described (Louis[29]), but the author has not been able to see the report. The bone marrow shows moderate hyperplasia. The brain may show non-specific degeneration of ganglion cells and at times a mild meningoencephalitis is seen. Ascites is frequent.

Symptoms. The onset of symptoms follows an incubation period averaging 3 to 4 weeks in the naturally occurring disease where knowledge of contacts has permitted measurement; in homologous serum jaundice the incubation period has averaged approximately 4 months. (See section on Etiology.) In sporadic cases no relationship to other cases may be established.[4] The clinical symptoms in naturally occurring and homologous serum jaundice are so similar that one description will suffice for both.

Symptoms may not occur at all. In epidemics symptoms without icterus and instances without symptoms but with evidences of silent hepatitis have been found.[18] Pollock[47c] has reported instances in small children which he believes to be symptomless attacks of infectious hepatitis. Final etiologic proof is lacking. When findings do occur the course and severity are variable. Three stages are, in general, recognized. A *pre-icteric* stage of prodromal symptoms before jaundice and hepatomegaly appear leads to an *icteric* stage in which hepatomegaly and jaundice are present. The icteric stage is followed by a stage termed *convalescent*, when the disease takes its usual course, or *final* in those few instances in which a fatal termination is imminent.

Pre-icteric Stage. In several large series[3,20a] this stage has been definite in 83% of the cases and lasts generally about 5 days. All grades of severity are seen, from mild to extremely prostrating symptoms. Anorexia may be the chief symptom. Epigastric distress, nausea, vomiting and weakness may appear. Abdominal distention and cramps also develop. Occasionally malaise or urticaria may be seen. Headache, constipation or diarrhea, and joint pains sometimes develop. In Bercovitz and Knoch's group, 13 of 54 patients had prior symptoms of upper respiratory infection. In Havens' series of 200 patients in the Middle East and in Bercovitz and Knoch's and Finks and Blumberg's groups, the frequencies of the symptoms are shown in the table.

At times the patient may complain of nothing except perhaps a feeling of being below par for a few days before jaundice is noted. His attention may be drawn to the jaundice by friends. In general, the type of onset varies greatly within the same group of cases. Most usual is the

insidious onset with anorexia, epigastric distress and dark urine. At times a more acute onset is more frequent. In 1 outbreak in the Lebanese Republic,[64] 70% of the patients had onset with chills and moderate fever which subsided in 4 to 5 days. In such instances the temperature usually drops with onset of jaundice, or 24 to 48 hours before. In a Canadian epidemic[54] the average patient had sudden onset with fever, anorexia, nausea and abdominal pain. Fever in such instances may go to 104° F. or more. Headache may be severe and vertigo and generalized body pains, particularly in the arms, neck and legs, occur. About one-half the patients in Havens' group had sudden onset with chills or chilliness and remittent temperature to 102° F. More usually fever, if present, is low grade. Finks and Blumberg[15] stress the occasional occurrence of fever in postvaccinal hepatitis and its frequent occurrence in their group. Similarly in the postvaccinal group incidence of dermatitis was high. Lymphadenopathy was found frequently in the naturally occurring group and is often not mentioned in the postvaccinal cases.

	Havens, percent.	Bercovitz and Knoch, percent.	Finks and Blumberg, percent.
Anorexia	82	88.8	87
Nausea	82	87.0	84
Weakness	75		
Epigastric distress	42		
Abdominal discomfort		37.0	
Vomiting		27.7	51
Generalized malaise		25.9	34
Diarrhea		11.0	33
Constipation		5.5	22

The interval from onset of symptoms to development of jaundice varies from 1 to 18 days. In approximately 75% jaundice appears by the 6th day. The average is often given as 5 days. Hepatitis may occur without the development of jaundice and the diagnosis is likely to be missed except in an epidemic. The liver may be enlarged and tender and lymphadenopathy may occur. Laboratory data may not be helpful and icterus indices may be normal as may the van den Bergh reaction. Urinary urobilinogen is increased and the hippuric acid test in Finks and Blumberg's[15] experience has been helpful.

Icteric Stage. After the onset of jaundice, or just before it appears, the temperature may become slightly elevated but not to the previous peak. The gastrointestinal symptoms persist and are likely to be accentuated. Anorexia may become severe and nausea and vomiting, if not present before, may develop. Distention and heaviness in the epigastrium are common. Right-sided abdominal pain may be accompanied by tenderness and simulate acute abdominal disease. The depth of jaundice varies greatly; it may be light or deep and the average duration is about 3 to 4 weeks, although periods of 5 to 72 days, or even longer, are known. It usually reaches its height before the 10th day and then begins to recede. In general, the symptoms of this period correlate with the icterus. Itching is not common with the jaundice. The stools may become light in color, often for a period averaging about 8 days, but are seldom typically clay colored. Lymphadenopathy has been found in as high as 81% of naturally occurring cases and at times may be a striking feature. The nodes varied from the size of a small pea to that of an English walnut. The size and consistency vary. Early in the disease they may be soft, non-tender and discrete. Later they become firm, smaller and shotlike.[15]

When jaundice fails to appear the clinical picture, though otherwise a typical one, is likely to be milder than usual and of shorter duration.

Final Stage. This stage occurs in those cases in which in the icteric stage events take a turn from the usual benign course

to a serious severe course resulting in death. In elderly patients and in pregnancy the disease is sometimes prolonged and the symptoms may be severe. It is apparently more apt to occur when the individual is in a state of malnutrition or exhaustion when infected. This stage is so infrequent in occurrence that it does not constitute a part of the average case. Here jaundice continues and even increases. Acute liver failure ensues. Nervous symptoms, lethargy or coma alternating with restlessness, excitement, delirium, muscle weakness, scanning speech and exaggerated reflexes usher in this phase which usually occurs before the 20th day of the disease, and most often within the first 10 days.

Convalescent Stage. This stage, rather than the final stage described above, usually follows the icteric period. In this period exercise is known to cause recurrence of symptoms and signs and graduated exercises are used as final criteria of clinical recovery. In about 10% of Barker's[3] cases, recovery has not taken place within a 3 months period.

Physical Findings. In the pre-icteric stage physical findings are not outstanding. Tenderness may develop in the right upper quadrant of the abdomen and hepatic enlargement is also usually present before jaundice appears. Splenomegaly and lymphadenopathy may appear in this stage. Lymphadenopathy has already been discussed. The outstanding finding of the icteric stage is, of course, jaundice. The liver, often already enlarged as stated above, increases in size usually to 3 or 4 finger breadths below the costal margin. It is reported as palpable in anywhere from 20 to over 70% of the cases. Splenic enlargement appears in 10 to 25% of the cases. In some epidemics[64] splenomegaly has been reported in one-third of the cases. Tenderness accompanies the hepatic enlargement in two-thirds or more of the cases and may be present when the liver cannot be felt. Hepatomegaly usually correlates with the progress of the disease, reaching its height, on the average, in 16 to 17 days and then starting to recede. Bradycardia is uncommon.

Changes in the skin are sometimes seen. These include erythema nodosum, urticaria, petechiæ and purpuric areas. Bleeding gums are also seen. In severe cases with a prolonged course, spider angiomata may appear. The final stage is characterized by an increase in icterus, coma and the neurologic findings stated above, at times a shrinkage in the size of the liver, and sometimes hemorrhagic phenomena such as epistaxis, hematemesis and hematuria.

The convalescent stage is characterized by a recession of the physical findings. Hepatomegaly may appear following exercise and occasionally jaundice may reappear for the same reason.

Laboratory Data. The laboratory data vary with the stage of the disease. In the *pre-icteric stage* measures of bilirubinemia, such as the icterus index and van den Bergh test, are normal except in the period immediately preceding the appearance of jaundice. Bilirubinuria occurs 1 to 3 days before clinical jaundice appears. One-half to three-quarters of the cases (Barker[3]) show a positive cephalin cholesterol flocculation test in this phase. At times the bromsulfalein and alkaline phosphatase tests may be abnormal. In this stage the blood sedimentation rate is not markedly elevated, a point held helpful by some in the differentiation of other states in which fever is associated with a rapid sedimentation rate.

In the *icteric stage* the icterus index is, of course, elevated. Figures to 100 or 150 are not uncommon and readings have been found over 300. In the 2nd to 3rd week, often about the 10th day, the icterus index starts down and usually is normal by the 5th or 6th week. The *van den Bergh reaction* is at first indirectly positive, but may change to a direct reaction as the icterus index elevates. *Urobilinogen* is found in abnormal range as the icterus index rises. The urine shows bile, as stated above, in the terminal phases of

the pre-icteric stage. Albuminuria of mild degree is not uncommon. Stools become light in color during the early part of the icteric stage and may persist as such until the height of the disease. Although many patients describe stools as clay colored, seldom are such stools actually present. The *prothrombin time* may be prolonged and, with severe liver damage, is not corrected by vitamin K therapy. As in the pre-icteric stage, the *cephalin cholesterol flocculation test* is positive in a high percentage of cases. The figure exceeds 90%. It is almost universally positive in patients with acute symptoms. It becomes negative in 3 to 4 weeks but at times may persist for 3 or 4 months. *Other evidences* of disturbed hepatic function may appear. These include changes in *blood proteins*, as reflected in actual measurements or in the *colloidal gold test*, depression in *serum amylase* followed by an elevation and retention of bromsulfalein. *Blood cholesterol* levels may be elevated. In general, the *glucose tolerance curve* is not markedly changed. In anicteric cases dye retention and the cephalin cholesterol flocculation test are most important, as are the other tests (aside from those for bilirubin) mentioned above.

The blood sedimentation rate is not markedly elevated. The white blood count is, in general, not elevated. Moderate leukopenia is often present, often starting in the pre-icteric stage. Atypical lymphocytes, often to 5 to 20%, similar in type to those seen in infectious mononucleosis, are seen.[36] Heterophilic antibodies are absent. In about 5% of the cases the white blood count exceeds 10,000.

Final Stage. In the few cases reaching the stage of acute yellow atrophy the white blood count is more likely to be elevated, even to 25,000. The usual findings of acute yellow atrophy are seen.

Convalescent Stage. This stage is heralded from the laboratory standpoint by a reduction in the blood bilirubin to below 2 mg. and the van den Bergh becomes indirect. The icterus index drops below 20 units. Likewise, the bromsulfalein retention is reduced.

DIAGNOSIS. The greatest difficulty in diagnosis occurs in the pre-icteric stage, although with the diagnosis in mind one may suspect its presence when anorexia, hepatic enlargement and hepatic tenderness appear. Evidence to diagnose the disease in the pre-icteric stage may be meager. This is particularly true in those instances with fever. Aside from malaria, other conditions to be considered in the differential diagnosis in this period include upper respiratory infections, atypical pneumonia, infectious mononucleosis, enteritis and influenza. In tropical areas besides malaria, sandfly fever and dysentery may be confusing. In an epidemic suspicion of the diagnosis is high and the laboratory findings already mentioned may be helpful in diagnosis. Pollock[47a] has found in the early stages a qualitative change in serum bilirubin with the appearance of small quantities of bilirubin in the urine. He found that the pre-icteric stage of the disease is characterized by an abnormal retention of bromsulfalein, the excretion of small quantities of bilirubin in the urine and the development of an abnormal direct van den Bergh reaction. The serum bilirubin and urine urobilin levels do not usually rise above normal limits until shortly before jaundice appears.

Hallock and Head[19] found that in troop concentrations the demonstration of pathologic amounts of urobilinogen in the urine was very helpful in 9 out of 10 patients in this stage. Gellis and Stokes[16] have shown that the methylene blue test for urobilinuria is positive in the pre-icteric stage. The cephalin flocculation test may also be positive in the pre-icteric stage. When fever is the problem in differential diagnosis Wood[63] found the sedimentation rate below 10 mm. in 85% of the cases, a point he felt useful in differentiating malaria. Repeated examinations for hepatomegaly and its appearance, together with tenderness, are most helpful. There is no specific test

for the disease, and other forms of hepatitis may be confused with it at this time. The diagnosis will not become certain until jaundice appears. In cases in which icterus does not develop the characteristic history and physical findings along with laboratory data indicated suggest the diagnosis, especially in an epidemic or when the examiner keeps in mind the fact that such an entity exists.

In the icteric stage diagnosis rests upon the elimination of infections, such as pneumococcic and streptococcic septicemia, malaria and syphilis, in which hepatitis is more or less incidental to systemic infection; other types of hepatitis in which the hepatic findings are the outstanding clinical features, such as yellow fever, leptospirosis, occasionally amebic hepatitis with jaundice, and infectious mononucleosis; and, finally, degenerative changes in the liver resulting from hepatotoxic chemicals, such as arsenic, carbon tetrachloride and cincophen. If jaundice does not appear in infectious hepatitis, hepatomegaly with tenderness will still demand differentiation of the above states.

In the convalescent stage diagnosis will rest on history, possible persistence of hepatic dysfunction, its recognition by laboratory means, the ruling out of similar states by such evidence as negative serologic reactions for leptospirosis and infectious mononucleosis, along with possible reactivation of the clinical picture by exercise.

Complications. In general, complications of infectious hepatitis are not common. Some of the so-called complications are actually less common clinical manifestations of the disease itself. This is true of nervous symptoms, such as numbness and weakness of the limbs, and meningeal symptoms early in the disease. Hemorrhage is in the same category. Likewise, in the final stage, described above, the picture of acute yellow atrophy appears, with mental excitement, convulsions and coma. Pulmonary, cardiac and gastro-intestinal symptoms are well established. As sequelæ to the disease, nephritis and cerebral hemorrhage are known. Relapse of the clinical picture occurs, particularly when exercise has been permitted too early in the convalescent stage. Commonly the convalescent stage is prolonged, especially if prostration has been marked. In some series,[3] 5 to 10% of the patients are not clinically well at the end of 3 months.

Recurrence of infectious hepatitis in the same patient is considered uncommon but does happen. In 1 series[13] only 4 individuals of 2614 had had more than 1 episode of jaundice. Nelson[45] reported 2 patients in whom 5 episodes of jaundice occurred and in whom he interpreted the episodes as recurrent infectious hepatitis. Inability to demonstrate the etiologic agent always throws doubt on the veracity of such reports despite elaborate means for differential diagnosis.

Stokes, Owen and Holmes[58] have found as have others that neurologic findings have been protean. They have found 4 main groups. First is the picture occurring in the fatal case with drowsiness, apathy, stupor, or maniacal symptoms, coma, and convulsions, symptoms found in all types of acute hepatic necrosis. Second occurs the symptom complex of generalized or localized muscular rigidity with increased tendon reflexes and at times choreiform movements. Striatal and pyramidal signs are outstanding. Third large focal hemorrhages may occur in nervous tissue and at times produce localizing signs. Finally, peripheral neuritis is described.

In epidemics in the Armed Forces[8] there have been men who, despite complete recovery as attested by laboratory data, continue to show fatigue, right upper quadrant discomfort, digestive disturbances, especially fat intolerance, malnutrition and emotional instability. Despite the lack of evidence of an organic lesion to account for these symptoms, the picture has shown a constant pattern.

Chronic, persistent, hepatic damage has been shown in a small number of cases. This may be manifested as a latent hepat-

itis[1,27,28] with persistent subclinical icterus and decrease in the bilirubin excretion test, in some patients years after attacks of infective jaundice. Symptoms, chiefly chronic gastro-intestinal complaints, have occurred, but often the disease is entirely latent. Bloomfield[6] believes that some such cases may gradually progress until eventually, perhaps after years, the clinical picture of hepatic cirrhosis appears. Others[49] find a history of jaundice in 6.5% of patients with cirrhosis and feel that possibly permanent structural liver damage may occur following such states. Although some discussion has been given these residual states, it must be remembered that the usual finding is complete recovery.

Prognosis. In general, the course of infectious hepatitis is mild and the prognosis excellent. The mortality rate is extremely low, usually being given as less than 0.5%. The natural history of the disease depends to a considerable extent upon the condition of the liver prior to the onset of the illness and upon factors which affect its capacity for regeneration during the course of the disease. Thus, in elderly patients the course is more apt to be long and serious. Sequelæ are more likely. Those with past liver damage and chronic alcoholism do not do well. In some outbreaks mortality has been higher in groups on less adequate diets.[62] In pregnancy the picture is often a severe one and may prove fatal. The development of the final stage or phase, with the picture of acute yellow atrophy, is thought to be more frequent when treatment has been neglected early in the disease, especially the neglect of rest.[3] Hemorrhage, especially with prolonged prothrombin time not responsive to vitamin K therapy is a serious sign.

Treatment. Early diagnosis and institution of treatment, especially in the pre-icteric stage, are thought to be most important. The foundations of successful treatment are rest and adequate diet. Army experiences with homologous serum jaundice (Turner[59]) and naturally occurring infectious hepatitis (Barker[3]) indicate the importance of rest. Patients who continue to work early in the disease do badly. Early bed rest decreases the severity of the disease and shortens the clinical and convalescent periods. Too early resumption of activity may result in recurrence, increased hepatomegaly and a return of symptoms. The same is true in patients in whom intercurrent infection of the respiratory tract occurs (Finks[15]).

Dietary therapy is most important. Generally it is stated that a high protein, high carbohydrate, low fat diet enhances the results achieved by rest. There is at times some dislike for excessively high protein (200 gm.) diets, and where a free choice of diet has been permitted patients usually prefer a diet of normal proportions. Under any circumstances the protein intake should not be low, and the carbohydrate intake should be high (400 gm.). Fat should be restricted. Anorexia may make for difficulty in intake of the proper diet. Frequent feedings are often helpful under these circumstances, but if nausea and vomiting make intake difficult intravenous glucose, 5 to 10%, is necessary. With protracted nausea and vomiting plasma or whole blood transfusion may be necessary to bolster protein intake. Two units of plasma a day will accomplish this end (Barker[3]).

From experimental data on liver protective diets, dietary supplements, especially multivitamin preparations, would seem proper therapy. Certainly with hemorrhagic phenomena associated with reduced plasma prothrombin levels, parenteral vitamin K in 2 mg. doses is in order. It and vitamin B_1 in excess have been thought harmful by some. The latter may be used in doses of 3 mg. daily by mouth. Adequate intake of other vitamins is indicated but their use in excess is not indicated. Alcohol is contraindicated. The known prophylactic value of methionine and choline in liver disease suggests their use in therapy. In general, they have not been shown to affect the

clinical course measurably.[25,55,59,62] Doses of methionine have been 5 gm. daily.

Pollock's[47b] studies of liver function in infectious hepatitis were gauged by the hippuric acid synthesis tests and indicate that the ability to synthesize hippuric acid bore some relation to the severity of the attack and showed improvement from the time of admission to the hospital, even though the icterus index and jaundice increased. He stated that it is probable that maximum liver damage in this disease most commonly occurs before the patient is admitted to the hospital. Specific treatment is, therefore, not likely to have any striking success unless begun in the pre-icteric stage.

Symptomatic and supportive therapy is applied as indicated. Morphine and barbiturates are to be used with caution because of the enhancement of their action in the presence of liver disease. Atropine or belladonna is helpful for abdominal cramps.

The criteria of Barker, Capps and Allen[3] as to when the patient may be allowed out of bed include at least 3 weeks of bed rest, normal liver size, or, if palpable, lack of tenderness, absence of symptoms, especially lassitude and anorexia, bilirubin levels normal for a week or, if elevated, under 2 mg. per 100 cc., or icterus index under 16, absence of a prompt direct qualitative van den Bergh reaction. They think it desirable for the bromsulfalein dye retention to be under 10% in 1 hour and better under 6%. After the patient is ambulatory, he should be examined for increased tenderness and enlargement of the liver which, if present, indicate further bed rest.

PREVENTION. The preventive aspects of infective hepatitis are not yet on sound practical grounds, for the epidemiology is not well established. Existing evidence that the patient is infectious in the pre-icteric stage also makes the problem of control difficult. Evidence that droplet infection and spread through intestinal excreta are important has already been discussed. Water-borne virus has been demonstrated (Neefe *et al.*[40]). Hence, measures to combat both of these routes of spread are in order. There is evidence that the complete inactivation of the causative agent in drinking water may require further modification of methods used for water disinfection (Neefe *et al.*[41]). No prophylactic vaccine has been developed. There is some promise in the use of immune globulin in prevention of the disease when epidemics exist (Stokes and Neefe[57]). Results thus far justify its trial under such circumstances; in some groups the routine use of 10 cc. on admission of men with previous transfusions is now being tried. The results have not yet been published. Effectiveness of immune globulin in prophylaxis has been confirmed in 2 field studies in the Mediterranean theatre (Gellis *et al.*[17a]) which suggest that the globulin confers a period of passive immunity of at least 6 to 8 weeks. Its use has also been confirmed in at least 2 institutional outbreaks in the United States. In 1, the case rate for jaundice in the controls was about 10 times that noted among those inoculated. It was effective when given in the incubation period, preferably earlier than 6 days before the onset of symptoms. In an outbreak in a home for children (Havens and Paul[21]) striking differences in occurrence of jaundice in inoculated and uninoculated groups were noted. Only 2 of 97 inoculated children developed jaundice and these appeared within 6 days of the administration of the gamma globulin. The long incubation period of the disease lends itself well to prophylactic injections. Doses used have varied from 0.06 or 0.08 cc. to 0.12 or 0.15 cc. per pound of body weight intramuscularly. Apparently (Gellis *et al.*[17b]) once the initial symptoms appear globulin is not helpful.

The prevention of homologous serum jaundice has been accomplished in part by the removal of human serum from the content of vaccines. In syringe transmitted hepatitis prevention can be accomplished by sterilization by dry heat (160° C. for 1 hour) of all syringes and

apparatus used for parenteral injections. Thorough physical cleansing of syringes is essential. Transmission by transfusion from donors before onset of symptoms (Murphy[37]) might be difficult to control (Snell *et al.*[55]) but certainly prospective donors with suggestive symptoms, with a history of hepatitis within the past year, with exposure to the disease within 3 months, or with transfusions themselves within the past 6 to 8 months should not be used. The possibility of using a donor when he is in the incubation period or subclinical stage is evident, especially in epidemics. The virus circulates in the blood probably for some weeks before jaundice appears. The possibility of "healthy carriers" has been brought out (Rappaport[48]). Recently a report has indicated that ultraviolet irradiation (Oliphant and Hollaender[46]) of serum containing the etiologic agent of homologous serum jaundice appears to inactivate it. This suggests that ultraviolet irradiation might be useful as a routine procedure in processing potentially icterogenic human serum or plasma.

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NEUROLOGY AND PSYCHIATRY

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SCHIZOPHRENIA

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Present day concepts of schizophrenia are largely based upon the formulations of Kraepelin, Bleuler and Meyer. Kraepelin[34] brought together a group of mental disorders, previously considered diverse in character, which he labeled "dementia præcox." The common features of these disorders comprised: (1) a lack of interest and emotional reactivity, and (2) a weakness of judgment or evaluation without impairment of memory. Kraepelin's dementia præcox was subdivided into the 4 types which are still commonly employed in psychiatric diagnosis: (1) simple dementia, characterized by progressive withdrawal and lack of interests; (2) hebephrenia, characterized by looseness of thought, silliness, and poorly fixed hallucinations and delusions; (3) catatonia, characterized by the presence of fixed postures and waxy flexibility; and (4) paranoid forms in which persecutory delusions predominate. Kraepelin assumed that dementia præcox was a degenerative disease of the brain or a metabolic disturbance and that the prognosis was uniformly poor.

Bleuler introduced the term "schizophrenia" which was based on his recognition of the absence of a true dementia and his concept of the "splitting of the psyche.[5] The "basic symptoms" of schizophrenia, as outlined by Bleuler, were: (1) disturbances of association of ideas leading to incomprehensible, incoherent productions; (2) disturbances in affectivity with emotional indifference or unnatural expression of emotion; (3) "schizophrenic ambivalence" in which mutually exclusive ideas exist side by side; and (4) lack of memory impairment.

Meyer,[41] unlike Kraepelin and Bleuler, was not convinced by the evidence in favor of the organic origin of the disorder. He emphasized the clinical picture not as a disease entity, but rather as a type of reaction in certain personalities as a result of a progressive difficulty in adaptation. He noted that no true dementia or deterioration as seen in organic brain disease was present but that the accumulation of faulty habits of reaction led to a "habit deterioration." By the schizophrenic reaction type (or parergasia, as Meyer preferred to call it) was meant "those disturbances developing in particular constitutional types and expressed in vague, autistic fancy, projections, passivity, paranoid systemization, formal disorders of language and behavior, incongruity of affect and motility disturbances." The attempt was made "to avoid any fatalistic concept, recognizing deterioration as an end-stage of certain cases only, but preferring to focus on factors of modifiability and potential re-synthesis."

Classification. Most recent writers recognize the futility of attempting to divide schizophrenic disorders into sharply demarcated groups. Kraepelin's classification has continued to be used in spite of the difficulty in forcing many cases

into 1 of his 4 types. While noting the impossibility of making rigid categories and recognizing the frequency with which a patient will shift from one pattern to another, Terry and Rennie[50] have nevertheless suggested a number of clinical reaction patterns which they felt could be profitably used in the study of schizophrenia: Group I. Aggressive reaction, associated with paranoid trends or hypochondriacal delusions. Group II. Conversion reaction, with fantastic experiences of rebirth, spiritual missions, and self-punishment or self-sacrifice. Group III. Passivity reaction, with obsessive-compulsive ritualistic behavior or with periods of stupor sometimes alternating with periods of excitement. Group IV, Deliroid reaction, with episodes of odd overactivity with deliroid features suggesting the influence of a toxic condition. Group V. Affective reaction, with emotional disorders, especially depression, either at the onset or occurring in cyclic form. Group VI. Defeatist reaction, with incongruous day-dreams and delusions, empty and vague thinking, and slovenly personal and social habits.

Hanfmann and Kasanin,[24] in a study of conceptional thinking in schizophrenia, found that their cases fell into the following 6 groups: (1) "Neurotic" schizophrenic cases, in which the schizophrenic reaction comes only as a last resort, when neurotic defenses (obsessive or hypochondriacal neuroses) fail. (2) Acute episodic psychoses with marked overactivity, extreme dramatization of conflicts in a setting of fairly good contact with reality, and a tendency toward clear intervals. (3) Cases with a paranoid tinge with mild ideas of reference and occasional hallucinations, frequently associated with a history of alcoholism and homosexual conflicts. (4) Cases of "primary thought disorder" in which there is a striking involvement of intellectual functions with marked incoherence and irrelevance. (5) "Cases showing marked dissociation with extensive compensatory fantastic elaboration with primitive archaic ideas of omnipotence coming to the surface, with the feeling of a certain mission in life that has to be performed, and with a variable regard for the ordinary realities of life." (6) Old cases of schizophrenia with ideas of reference and delusions of persecution associated with little emotional reaction to these ideas.

Etiology. No general agreement has been reached as to either the homogeneity or the etiology of the schizophrenic reaction. The trend in this country is to stress psychogenesis, although heredity and constitution, neuropathologic changes, and disturbances in biochemistry and physiology are still actively discussed as pathogenic features.

Sullivan,[49] for one, has questioned the unity of these disorders. He expresses the belief that 2 etiologically different reactions are included. One is characterized by an insidious development and a poor prognosis with signs and symptoms pointing to an organic degenerative disease. Sullivan is content to retain the Kraepelinian term, dementia præcox, for this group. He restricts the term schizophrenia to cases which he feels are primarily a "disorder of living" and without organic substrate. "The person concerned becomes schizophrenic as one episode in his career among others, for situational reasons, more or less abruptly. He may have had months or years of maladjustive living . . ." These patients are capable of recovery.

Meduna and McCulloch[40] have pursued a different course in dividing the schizophrenic disorders, largely neglecting psychogenic considerations. They recognize a "true" schizophrenia in Bleuler's sense with: (1) a disturbance of associations or weakness of judgment; (2) loss of interest and effect; and (3) lack of defect in perception, orientation and memory (sensorium). The onset in these cases is said to be insidious and the outcome characterized by progressive impairment of the mental and emotional life. Another group, labeled by Meduna and McCulloch as "oneirophrenia," is characterized

by a more or less acute onset with the symptomatology similar to the first group except for the impairment of the sensorium with confusion and disorders of perception and recollection. The symptoms are reversible, and the prognosis is generally good. This disorder is said to be due to a disturbance in carbohydrate metabolism (see below).

It is not entirely clear, but seems possible that Meduna and McCulloch's "schizophrenia" corresponds to Sullivan's "dementia præcox" and their "oneirophrenia" to Sullivan's "schizophrenia." What is to Sullivan a "disorder of living" is to Meduna and McCulloch a "disorder of carbohydrate metabolism."

HEREDITY. It is inevitable that lack of agreement regarding etiology and classification should be accompanied by divergent opinions regarding heredity. The most exhaustive recent study of heredity in schizophrenia is that of Kallmann,[29] whose material included 1087 schizophrenic patients admitted to the Berlin-Herzberge Hospital between 1893 and 1902 with their 3279 parents, husbands and wives, 3384 direct descendants, 3920 brothers, sisters, half-brothers and half-sisters, and 2194 nephews and nieces. One gains the impression that the author has set about his task with the intent of proving something of which he had already convinced himself. This may perhaps be gathered by a preliminary statement, "The principal aim of our investigation was to offer conclusive proof of the inheritance of schizophrenia . . ."

According to Kallmann, the probable incidence of schizophrenia among the offspring of schizophrenics is 19 times greater than in the general population. The grandchildren, nephews and nieces are about 5 times as likely to become schizophrenic as the average person. Qualitative biologic differences were found between the hebephrenic and catatonic types (the "nuclear" group) and the paranoid and simple types (the "peripheral" group), the simple type including cases with a mild, episodic course without marked tendency to deterioration. The expectation of schizophrenia for an undifferentiated group of schizophrenic offspring of schizophrenic patients was 16.4%, for siblings 11.5%, for half-sisters and half-brothers 7.6%, for nephews and nieces 3.9%, and for grandchildren 4.3%. In the "nuclear" group the expectancy figures are 20.9% for offspring and 12.9% for siblings, the first figure being about double and the second about $1\frac{1}{2}$ times the corresponding rates in the "peripheral" group. Kallmann expresses the belief that the pathogenesis of schizophrenia represents a complex, though specific, hereditary process. He assumes that the genotype of schizophrenia is a single recessive trait, penetrating with a probable manifestation of about 70%. "The mode of manifestation seems to depend on the total constitution, which probably determines the disease form in the individual and is in turn conditioned by special hereditary factors." Kallmann's statistics led him to the conclusion that no biologic or hereditary relationship exists between schizophrenia and other abnormalities such as epilepsy, neurosyphilis, feeblemindedness, alcoholism and criminality.

Kallmann advises the employment of extensive eugenic methods for eradication of the disorder. Sterilization of schizophrenics themselves would prevent but 1.7 to 3.4% of the total number. Eugenic prophylaxis should therefore be directed toward the tainted families; in certain cases there should be legal power to intervene. The "establishment of State archives of the tainted families" is also recommended.

Barahal,[3] in a brief study, agrees with Kallmann that the genetic analysis of schizophrenia shows a recessive inheritance of the main gene concerned, "but an irregular expression of the gene due to the modifying effects of both secondary genes and various environmental influences." He believes that while mental hygiene, psychotherapeutic and shock measures should be utilized, schizophren-

ics and their closest blood relatives should be discouraged from bearing children.

Pollock, Malzberg and Fuller,[44] using data derived from the New York State psychiatric hospitals, agree that schizophrenia arises more frequently in tainted families. They state that the type of psychosis, whether schizophrenic or manic-depressive, is more related to family history than to the precipitating situation. Malzberg[38] believes, however, that a single recessive factor, as suggested by Kallmann, does not adequately explain the inheritance. The fact that in Kallmann's study the incidence of schizophrenia in offspring is greater than in the siblings, has also led to the denial of the recessive character of the heredity and the postulation of a dominant characteristic (Mayer-Gross and Moore[39]).

Terry and Rennie,[50] in a comprehensive study of 77 patients, were impressed with the role of familial incidence in the background of their patients. The study lacks, however, any control material. In only 4 cases was no abnormality reported in the background. In 61 cases there was some type of familial psychiatric disorder; in 40 of these the disturbance was in the parents. The parents had actual psychoses in 23 cases, but in only 5 of these was it schizophrenic. In 29 cases there were actual psychoses in atavistic or collateral relatives. In an additional 12 cases, 1 or more relatives exhibited various character abnormalities. The authors conclude, "In considering the constitutional make-up of our patients, we are forced to accept the evidence of familial instability as well as to realize that these psychotic and unstable relatives contribute to the insecurity of the environmental background in which these patients were developing."

Psychogenesis. In Terry and Rennie's evaluation of 77 patients[50] with detailed case studies, environmental factors "emerge as extremely important in the development of personality features that make for difficulty. Equally evident is the fact that their families fell into extremes of solicitude and over-attention on the one hand and, on the other, states of nagging, pushing and comparison with better-adjusted siblings calculated to increase the gap between this child and the others or the outside world. Difficulties between the parents or the deprivation of a parent seems to contribute further to the insecurity of these children. The parental make-up is extremely important, and we find a large number of these children with the added disadvantage of daily contact with psychotic, eccentric, or emotionally unstable parents. A prominent feature of the family constellation is the pushing and nagging to which these children were exposed in an attempt by their families to have them reach the achievements for which they were not equipped, or an attempt to keep them apace with more gifted or successful brothers and sisters. In these children we find ample evidence of childhood instabilities being further subjected to environmental stresses making for increased uncertainty, insecurity and instability. It is impossible to study this material without being impressed by the importance of the family constellation and of the effects of maladjustments within the family in contributing to the growing timidities and insecurity of the children."

Of the 77 patients, 60 showed states of dependence on family overmanagement or overattachment to the family. Of the 60, 52 exhibited such childhood difficulties as enuresis or "delicate health." Of the remaining 17 patients, all but 1 showed evidence of family difficulties such as undue emotional attachment, poor emancipation, negativistic attitudes or poor adjustment to loss of a family member. The mother played the most significant rôle in the overdependence, somewhat more frequently in the male patients than in female patients. Presumably associated with the frequency of family dependency, resentment states, and difficulties in achieving emancipation, 71 of the 77 patients never attempted or had difficulties with ventures outside the family (scholastic, occupational, marital). Per-

sonality difficulties were accentuated in marriage. Difficulties and inadequacies were evident in the sexual sphere in 58 cases. Of these patients, 34 were either aloof or deliberately avoided contact with the opposite sex. In 22 cases autoeroticism was a focus of anxiety, while homosexuality played a similar rôle in 15 cases.

Fromm-Reichmann,[14] choosing to ignore or minimize constitutional factors, explains the development of the schizophrenic state on the basis of early infantile traumatic experiences, in contrast to those occurring in later childhood as found in psychoneurotics. "We think of a schizophrenic as a person who has had serious traumatic experiences in early infancy at a time when his ego and its ability to examine reality were not yet developed. These early traumatic experiences seem to furnish the psychologic basis for the pathogenic influence of the frustrations of later years." Such early traumata inflict greater damage on the personality than those occurring later.

"In addition, early traumatic experience shortens the only period in life in which an individual ordinarily enjoys the most security, thus endangering the ability to store up, as it were, a reasonable supply of assurance and self-reliance for the individual's later struggle through life. Thus is such a child sensitized considerably more towards the frustrations of later life than by later traumatic experience. Hence, many experiences in later life which would mean little to a "healthy" person and not much to a psychoneurotic, mean a great deal of pain and suffering to a schizophrenic. His resistance against frustration is easily exhausted. Once he reaches his limit of endurance, he escapes the unbearable reality of his present life by attempting to reëstablish the autistic, delusional world of the infant, but this is impossible because the content of his delusions and hallucinations are naturally colored by the experiences of his whole lifetime."

NEUROPATHOLOGY. In spite of many years of observation, no consistent abnormalities in brain structure have been noted. The studies of early neuropathologists, especially Alzheimer, showing cortical ganglion cell degeneration and fatty deposition have been verified by some recent observers and refuted by others. The attitude toward the histologic findings seems more determined by the training and orientation of the observer, whether he is neuropathologically or psychologically inclined, rather than the actual evidence.

The confused thinking in this regard is well illustrated in Hassin's textbook of neuropathology.[23] He introduces the subject by stating, "The several clinical forms of the mental disorder known as schizophrenia or dementia præcox are considered organic diseases of the brain, and not functional disorders . . ." This is followed by a description of a variety of pathologic observations "not uniform or typical enough to enable one to make a diagnosis under the microscope," including ganglion cell changes in third, fifth and sixth layers of the cortex, occasional foci of gliosis and accumulation of lipoids. In contrast to the preliminary assumption, Hassin concludes, "It is rather significant that regardless of the enormous effort and time spent on the study of the pathology of dementia præcox, the results are insignificant. . . . It is questionable, whether even the changes described above are not secondary, due to the long duration of the disease with its unavoidable somatic complications."

A number of reports have appeared recently concerning patients with schizophrenic syndromes in which definite and severe neuropathologic features were found at postmortem examinations. One of the most interesting is that of Holt and Tedeschi.[25] The patient had been in a state hospital in 1924 for 5 months with the diagnosis of catatonic dementia præcox and was discharged as completely recovered. Eighteen years later he again developed a severe catatonic episode and died. There were no abnormal neurologic findings during his illness. Histologic studies

disclosed a primary demyelinating process characterized by sharp demarcation and limitation of lesions to the cerebral white substance. Polatin *et al.*[43] describe 2 patients, hospitalized over long periods of time for schizophrenia, who showed signs of cerebral atrophy in pneumo-encephalograms and degenerating nerve changes on biopsy study. Interestingly enough, 1 of the patients was improved following electric shock therapy.

Roizin *et al.*[46] report an acute symmetric demyelinating process in a woman who died after a brief acute psychosis resembling catatonic schizophrenia. "The relationship between the clinical symptoms and the pathologic changes is emphasized not to create an organic concept of schizophrenia but merely to illustrate that a demyelinating process acting as a somatogenic factor may precipitate, in certain cases, an acute mental syndrome, which may or may not be associated with fleeting neurologic symptoms, the evaluation of which is at times difficult." The authors postulate that certain individuals have a constitutional predisposition to react with schizophrenic pattern whether the precipitating stimulus be psychogenic or organic disease of the brain. They suggest that the 1924 catatonic episode of Holt and Tedeschi's case was precipitated by psychogenic stimuli and the later catatonic episode by the demyelinating process.

Ferraro, quoted by Roizin *et al.*, has emphasized that the following possibilities must be considered where pathologic changes are discovered in cases of schizophrenia: "(*a*) The changes may be the expression of organic complications in the course of schizophrenia; (*b*) the changes may be the expression of a primary organic disease; (*c*) the changes may be the expression of the composite picture, in which soma and psyche integrate each other. The acceptance of the first or the second possibility may be confusing or misleading unless the third possibility is first evaluated and accepted or discarded. The third interpretation stems out of the concept that schizophrenia must be viewed from the standpoint of psychosomatic integration. The organic cerebral change could therefore be considered neither as the cause nor the complication of schizophrenia, but as the result of interplay of soma and psyche in the determination of the structural pathologic process."

Biochemistry, Physiology. Chemical studies of isolated blood constituents have not resulted in significant contributions to the understanding of the schizophrenic process. Recently, but few such studies have appeared. Katzenelbogen and Snyder[32] have analyzed the blood serum for sodium, potassium, calcium, magnesium and inorganic phosphorus and chloride and found no significant differences as compared with a control group. The blood bromine content has been found to be lower in schizophrenic subject (0.55 mg. %) than in normals (0.81 mg. %) (Wikoff *et al.*[53]), but no suggestion is made concerning the significance of the finding. Limited progress appears to have been made, however, utilizing more dynamic, physiologic methods.

Katzenelbogen *et al.*[31] studied the dextrose content of arterial (femoral) and venous (internal jugular) blood. They found the dextrose values of both the arterial and venous blood to be lower in their group of schizophrenics than in a normal control group. However, the difference between arterial and venous dextrose values was greater in the schizophrenics than in the controls. The authors suggest that at least certain schizophrenic patients have a lower carbohydrate metabolism than normals. The higher differences in dextrose between arterial and venous blood, however, suggest a more intense carbohydrate metabolism in schizophrenics. Some of the patients had a lower oxygen content of arterial and venous blood and a lower arterial-venous difference in oxygen than in a control group, indicating a diminished intracranial oxygen metabolism. The average arterial-venous difference in carbon dioxide content was also lower. Such analyses are of limited value in

view of the small number of patients studied (12), the lack of significant deviations and statistical control, the paucity of clinical data, the conflicting results, and the fact that the control group of "normals" was collected by other workers (Gibbs *et al.*).

Horvath and Friedman[26] noted a delay in the hypoglycemic effect and the subsequent recovery after intravenous administration of insulin in schizophrenic patients when compared with normal subjects. Glucose tolerance curves were found by Proctor *et al.*[45] to have an abnormally prolonged interval before returning to fasting levels, indicating a decreased glucose tolerance. These curves tended to return to normal following recovery, regardless of the type of therapy employed. Patients with apparent recoveries in whom the glucose tolerance curve did not improve often relapsed and the authors feel that the test may be of some prognostic importance.

The cases with acute onset with clouding of consciousness described by Meduna and McCulloch[40] as "oneirophrenia" (see above) are said by these authors to be associated with a disordered carbohydrate metabolism. This disorder is characterized by a diabetic-like Exton-Rose glucose reaction, a slow return to normal of the blood sugar curve, resistance to insulin, and an abnormally large output of an anti-insulinic factor in the urine. (Meduna had previously shown that 60% of schizophrenic patients had an anti-insulin factor in their blood.) The carbohydrate metabolism returns to normal with the disappearance of symptoms. It is apparently assumed by these authors that the metabolic defect is the causative factor.

Gellhorn,[17] on the assumption that schizophrenia is associated with deficient reactivity of the sympathetic nervous system, has attempted to show that all "successful" treatments of schizophrenia are effective because of stimulation of the sympathetico-adrenal system. This is said to be accomplished for the most part by the production of a lowered oxidative metabolism of the brain. That a relative anoxia leads to increased sympathetic discharge is shown by the rise in systemic blood pressure that occurs upon breathing a gas mixture low in oxygen. Gellhorn's experiments show that insulin hypoglycemia diminishes cerebral oxygen consumption and thus leads to sympathetic stimulation. Metrazol, even when convulsions are eliminated by curarization, acts similarly. The combination of hypoglycemia and oxygen deficiency produces greater sympathetic stimulation than even complete asphyxia. "If, as has been shown, successful treatment of schizophrenia is in essence due to nothing other than strong and lasting excitation of the sympathetic division of the autonomic system, involving profound alteration in the oxidative metabolism of the brain, it is to be expected that deficiency in the reactivity of the sympathetic system is a basic feature of schizophrenia."

In a later study Gellhorn *et al.*[18] find that normal and schizophrenic patients have the same amount of insulin and glucose in the blood in the absence of emotional excitement. During emotional excitement, however, the insulin content of the blood is greatly increased in psychotic patients and in most instances the blood sugar remains unchanged. When the blood is injected into a test animal, the increased insulin concentration leads to a marked fall in blood sugar and coma. Normal persons, on the other hand, show a slight rise in blood sugar with emotional excitement and their blood produces no hypoglycemic reaction in the test animal. "The experiments are interpreted to mean that the balance of the autonomic centers in psychotic patients under emotional stress is shifted toward the vago-insulin side whereas in normal persons the sympathetico-adrenal system greatly predominates." These findings and conclusions are not at all consistent with those of Horvath and Friedman, Proctor *et al.*, and Meduna and McCulloch and require further validation.

A number of investigators[19,21,22] have

noted nitrogen retention in patients suffering from periodic attacks of catatonia with normal nitrogen balance in remissions. This is said to be on the basis of faulty liver function. Liver function, as measured by the hippuric acid test, was found to be impaired in catatonic patients, while undisturbed in other schizophrenic and normal subjects.

A group of workers at Worcester State Hospital have brought together a body of physiologic data in an effort to broaden the psychologic concept of schizophrenic withdrawal to include physiologic phenomena. Schizophrenic withdrawal is defined as a state in which "the vital relations between a person and his physical and social environment become less intense and less numerous." They state that physiologic hyporeactivity is found in the general metabolism, functions of the autonomic nervous system, and functions of the central nervous system. The schizophrenic patient has (1) a lowered response to administration of thyroid;[8] (2) a reduced thermal response to dinitrophenol, a general oxidative stimulant;[9] (3) a lowered blood pressure and pulse rate response to the intravenous administration of epinephrine hydrochloride;[10] (4) diminished responses in blood pressure, pulse and respiratory volume as a result of blocking heat loss from the lungs by breathing hot, moist oxygen;[12a] (5) depression of the amount and of the duration of nystagmus as a result of vestibular stimulation[1] and significantly less sway following rotation than normal subjects;[12b] and (6) resistance to insulin.[11] In summary, Angyal, Freeman and Hoskins[2] note, "We are not prepared to state whether psychologic withdrawal is caused by a physiologic withdrawal (hyporeactivity) or *vice versa*. It is probable that neither is the case, but that one is dealing with withdrawal of the total personality manifested in a variety of psychologic and physiologic characteristics."

Psychologic Studies. Recent studies of the disorders of thinking and language in schizophrenia, while not solving the problem of etiology, have contributed to the understanding of schizophrenic behavior.

Cameron[7] has made an experimental analysis of the disorders of thinking and language in schizophrenia. This analysis leads him to describe as characteristic of schizophrenic disorganization: (1) Asyndetic thinking: This is marked by a lack of essential connections in the use of language. In place of well-knit sequences, the schizophrenic gives only a half-organized collection of fragments. (2) Metonyms and personal idiom: Unprecise substitute terms or phrases are used in place of exact terminology. (3) Interpenetration of themes: Parts of one theme appear as intrusive fragments in another unrelated theme. "Such a situation, in which a patient's asocial fantasy themes are able continuously to subordinate all external events in the field of social behavior, provides the patient with only a distorted and fragmented environment, which cannot possibly influence his conduct in a socially organized way." (4) Overinclusion: "These disorganized schizophrenics could not manage the essential first step in problem solving, that of narrowing down one's operations to something restricted and unified enough to call out organized attitudes and specific responses." (5) Incongruity between acts and words. (6) Altering the experimental conditions of psychologic tests: "It is suggested that this trend may be related to the patients' general inability to deal with facts as they are and to their tendency, when difficulties arise in the social field, to fall back upon some substitute in fantasy." (7) Generalizations varied but ineffectual. These generalizations concerning the solution of psychologic test problems were not useful because they were either too inclusive, too involved or too entangled with fantasy.

Deterioration. Dementia and deterioration have generally been employed synonymously and have usually implied a permanent impairment of intellectual function. Progressive intellectual deterio-

ration was to Kraepelin an essential feature of "dementia præcox." Though denied as inevitable by Meyer, Bleuler and other psychiatrists during the early portion of the century, the concept of deterioration has continued to be commonly accepted as a definite feature of at least certain cases. Numerous psychologic studies during the past 30 years have shown that the disturbance in thinking observed in the schizophrenic process is not identical with that seen with organic brain disease or feeblemindedness and that the disturbance is not necessarily an irreversible one. Among some of the more recent discussions of deterioration in schizophrenia are those of Kendig and Richmond[33] and Cameron.[7]

The study of Kendig and Richmond is based on an analysis of the psychologic examinations given at St. Elizabeth's Hospital during a 15 year period. The median mental age of the schizophrenic group was 11 years 5 months, about 2 years below the norm for the general population. They noted that the patients as a group showed inferior learning ability even during their school years. This difficulty could not be accounted for on the basis of early onset of the psychosis. "Bringing together these specific findings, our general conclusion is that the dementia præcox mind is blunted and dulled. This intellectual inferiority is not primarily due either to deterioration or to temporary impairment resulting from the psychosis, since it shows itself in extensive school failure long before the actual breakdown and, in most cases, before the occurrence of the first premonitory symptoms of the disease. While in some instances it may be congenital, our case histories suggest that more often it is the product of the emotional maladjustments which later play an important etiologic rôle in the precipitation of the psychosis." Whether or not the basis for school difficulties is of congenital origin or due to emotional conflicts, the problem remains the same. "A personality inadequate to meet the everyday exigencies of life may, as the stress becomes greater with the years, tend to escape, or be precipitated, into psychosis. This amply explains our test findings without implying any reduction in intelligence resulting from the disease, and thus saves us from the necessity of hypothecating somatic changes." Reexamination of 41 schizophrenic patients with the Stanford-Binet test after prolonged hospitalization indicated no progressive decay of function. In most of the patients a gradual recovery in the intellectual sphere corresponding with improvement of psychotic symptoms was noted.

Cameron[7] has shown that the disorganized thinking of schizophrenics does not follow the pattern of either deteriorated senile patients or of normal children. Lehrman,[35] who concluded that schizophrenic "deterioration" was neither inevitable or irreversible, suggests that the term be reserved for those patients suffering, not from schizophrenia, but from organic brain disease.

Conceptual Thinking and "regression" hypotheses. Attempts have been made to relate the schizophrenic thinking disorder to some basic concept. One of these is the concept of "regression" to either the level of primitive man or to the level of early childhood. One of the best known descriptions of regression to primitive levels in schizophrenia is found in Storch's "The Primitive Archaic Forms of Inner Experiences and Thought in Schizophrenia."[48] Storch found great similarity between the experiences of schizophrenic patients and those of various primitive people. He conceived of modern man as having a "rational superstructure" which, as the result of a "conflict of instincts of constitutional nature" (such as perverted sexual attitudes), crumbles; and primitive magic-archaic modes of behavior and thinking well up from the substrata. Others more recently have stressed such regressive characteristics as typical of schizophrenia, including Osborne[42] who suggested that the term schizophrenia be changed to

"palæophrenia." Others have suggested regression to a childhood level. Gardner,[16] for instance, has equated psychotic symptoms with childhood behavior and measures the regression in terms of "psychotic age."

Goldstein[20] has distinguished between abstract and concrete behavior. The concrete attitude is realistic and bound to the immediate experience of the given thing or situation. The abstract attitude, however, passes beyond the given specific thing or situation which then becomes merely a representative of a category. Hence the latter type of thinking is also called the categorical or conceptual attitude. Goldstein, Piaget, Vigotsky and others have concluded that childhood thinking is concrete and that the abstract attitude develops ordinarily after puberty. Goldstein has also shown that loss of abstraction occurs with organic brain disease (as discussed in a previous review[37]).

Vigotsky[52] studied concrete and conceptual thinking in schizophrenics by means of a block test devised by Ach. Blocks of different colors, sizes and shapes were used which the subject was to sort into 4 different categories. This sorting required the subject to form and test a number of theories or concepts. Vigotsky found that schizophrenics lacked the capacity to carry through the procedure successfully. He therefore postulated the loss of conceptual thinking as the basic psychologic disturbance in schizophrenia. Reminiscent of Storch, he conceived of the mind as being composed of an "old" substructure of concrete thinking, and of a "newer" outer layer of concepts. The latter portion of the structure is involved in schizophrenia. To Vigotsky, childhood, organic brain disease, and schizophrenia have in common the lack of ability in forming concepts. He therefore concluded that schizophrenia is an organic brain disease.

In this country, Hanfmann and Kansanin[24] have continued and amplified Vigotsky's work with the Ach test. They agree that conceptual thinking is impaired in certain schizophrenics but believe that a transition from the highest conceptual level to the lowest primitive level of thinking is found, thus denying the simple dichotomy between the two as expressed by Vigotsky. The highest conceptual level of thinking demonstrated by the block test is found only in Hanfmann and Kasanin's college educated group, while the non-college group scored only at an "intermediate level." When schizophrenic patients were compared with normal subjects with comparable educational background, defects in concept formation were noted, but only in a portion of the schizophrenic group. Definite impairment was found in 26 of 62 subjects. It was found most commonly in patients classified by Kasanin as "primary thought disorders" (see above), and in the groups marked by dissociation with fantastic elaboration of ideas and in those with paranoid-hebephrenic trends with dull affectivity. Schizophrenic patients with neurotic traits tended to have little or no impairment in conceptual thinking.

Goldstein[20] has recently applied the methods he had previously used in studying patients with organic brain defects to schizophrenic patients. He agrees that concrete thinking as opposed to conceptual or categorical thinking is found in a certain number of schizophrenics. Goldstein points out that regardless of the differences in normal individuals in abstract thinking, they can learn by demonstration to proceed along an abstract way. The schizophrenic, however, cannot learn to do so. "Many of the peculiarities of the behavior of schizophrenics become understandable, when considered as expressions of a greater concreteness. Concrete behavior means that in our behavior and activity we are governed, to an abnormal extent, by the present outer world stimuli and by the images, ideas, and thoughts which act upon us at the moment. On the one hand, symptoms arising from this atitude are autistic thinking and acting, and on the other hand, abnormal boundness to outer world stimuli as far

as they belong to that realm of reality which the patient experiences. The world of the schizophrenic is determined to a pathologic extent by his own feelings and thinking, and by his capacity to react. The demarcation between the outer world and his ego is more or less suspended or modified in comparison with the normal. Here is one origin of illusions. The objects which impress the patients are not the same as those which would impress the normal person in the given situation. He experiences only objects to which he can react in the only way in which he is capable, *i. e.*, in the concrete way."

Hanfmann and Kasanin and Goldstein point out that the loss of abstract thinking found in both schizophrenic and organic brain disease is not necessarily proof of an organic origin of the schizophrenic process. Goldstein notes certain differences between the 2 groups. In the organic group, disintegration toward the concrete is of a simplified and inane form but more or less obvious to the observer. The concreteness of the schizophrenic is different, inasmuch as his thinking is richer and animated with more personalized ideas. While the similarities between the 2 groups suggests that a somatic factor is involved, the defect could also be considered as a retreat from an unbearable conflict.

Benjamin (see Kasanin[30]) has studied the thinking in schizophrenic subjects by having them interpret a series of proverbs:

"1. When the cat's away, the mice will play.
2. Don't cry over spilt milk.
3. It never rains but it pours.
4. The burnt child dreads the fire.
5. Don't cross your bridges till you come to them.
6. A rolling stone gathers no moss.
7. Discretion is the better part of valor.
8. To fiddle while Rome burns.
9. Don't count your chickens until they're hatched.
10. The proof of the pudding is in the eating.
11. He who laughs last, laughs best.
12. New brooms sweep clean.
13. Ingratitude, thy name is woman.
14. He travels swiftest who travels alone".

Completely literal (concrete) responses, such as "It doesn't stay long enough in one place" as the response to the sixth proverb, are found much more commonly in intelligent schizophrenics than in mildly defective non-schizophrenics. Such responses are found only in schizophrenia, organic brain disease and mental deficiency. False symbolizations are also commonly noted in schizophrenics, as "a person who brags all the time never gets anywhere" in answer to proverb No. 6.

Kendig and Richmond,[33] and Cameron do not believe, however, that the loss of conceptual thinking is the basic characteristic of the schizophrenic state. The former has not found defects limited to this sphere, but rather present in all tests requiring sustained effort and attention. Cameron has found that even severely disorganized schizophrenics are capable of abstract attitudes when adequate coöperation is obtained. He is critical of the rigid interpretations required by Hanfmann and Kasanin in the Ach block test; he believes that while the patients' interpretations may not agree with those of the examiner, they nevertheless may still be generalizations. "There is good reason for doubting the usefulness, to say nothing of the validity, of these determined efforts to maintain separate categories of 'abstract' and 'concrete' behavior. The notion is based upon an equally hypothetical differentiation between 'perceptual' and 'conceptual' thinking; and upon inspection this will be found to reduce to little more than the ancient narcissistic flattery that granted rationality to adult human thought but denied it to children and animals—some stoutly denied it to women also." "The fact that schizophrenic disorders do appear among adults in 'primitive' (*i. e.*, non-technologic) civilizations and among young children of our own contemporary technologic civilizations, as well as the results of comparisons that have been made between the logic of normal children and adults and that of schizophrenics, contradicts the regression hypotheses. Moreover, the contention is supported by the same evidence that schizophrenic disorganization represents

neither a retracing of the ontogenetic-phylogenetic path of development, nor a removal of outer layers of thought to expose any 'primitive nucleus.' Instead, it presents us with a development, new and unique for a given individual's life history, that can be made quite intelligible in behavioral terms."

The schizophrenic, according to Cameron, is essentially "disarticulated" from the social group. The normal person gradually acquires language behavior and thinking which can be shared and compared with others and by which he learns to be self-critical. He feels that disorganized schizophrenics are persons who have not developed adequate role-taking skills, who have a history of social inadequacies, and who have been unable to establish themselves firmly in their cultural patterns. Faced with emotional conflicts and disappointments, they progressively withdraw from social participation into fantasy.

Sullivan (see Kasanin[30]) has emphasized that the language of the schizophrenic is not meaningless, but has meaning only to those with an intimate knowledge of him. The language of the schizophrenic is not adequately censored by the patient or, as Sullivan puts it, lacks "consensual validation." This language defect is reminiscent of the language of dreams or the speech of very young children. The schizophrenic employs speech in a magic, autistic way in order to counteract his feeling of insecurity.

The Rorschach test, in which a series of standardized ink blots are interpreted by the patient, has been useful as a diagnostic adjunct and has contributed additional information concerning the personality structure of the schizophrenic. Because of the technical nature of the test, the subject cannot be adequately reviewed here. Some of Beck's conclusions,[4] however, may be cited. He takes to task 2 long accepted generalizations, first that schizophrenics have a rich life in fantasy and secondly that the schizophrenics have shallow emotions. From Rorschach test performances Beck shows that what has been conceived as fantasy is really distortion, misconstruction and inaccuracy, but not fantasy in the sense of a new creation. The emotions of the schizophrenics are not shallow but often exaggerated and poorly controlled.

THERAPY. In contrast to the numerous and diverse publications dealing with "organic" therapies for schizophrenia, the field of psychotherapy is marked by a paucity of recent contributions. This situation does not adequately reflect the actual status of psychiatric practice in many of the outstanding psychiatric institutions in this country. The writing of the numerous articles concerned with "organic" therapies has been promoted by the ease with which large groups of patients are collected, the appeal of new and rather easily learned treatments, and the rapid and dramatic response of many patients. While the various shock therapies have been generally accepted as worthwhile therapeutic adjuncts, they have not as yet contributed a great deal to our understanding of schizophrenia. Sullivan,[49] looking upon both psychoneurosis and schizophrenia as the outcome of difficulties in interpersonal relationships, stresses a similar therapeutic approach in both modified to the needs of the individual patient. He objects strenuously to the various "organic" treatments on the grounds that they reduce "the patient's capacity for being human," a fact that has not been verified for the shock therapies. Fromm-Reichmann,[14] whose thesis of the origin of schizophrenia as the result of psychologic traumatic experiences in early childhood has already been noted, also stresses that analytical procedures may be profitably employed. The patient must feel comfortable and secure enough to give up his narcissistic isolation and to use the physician for resuming contact with the world. "It is certainly not an intellectual comprehension of the schizophrenic but the sympathetic understanding and skillful handling of the patient's and physician's mutual relationship that are the decisive therapeutic factors."

The 2 most frequently employed shock therapies, insulin coma and electrically induced convulsions, have been previously described in this section[27,53] and elsewhere and will not be discussed in detail here. The report of Bond and Rivers[6] is representative of the results with insulin shock therapy. In a control group of 100 patients not treated with insulin shock, 16 were recovered or much improved after hospitalization; 14 of these were well at the end of 6 or 7 years. Of 251 schizophrenic patients treated with insulin shock, 138 (54%) were recovered or much improved at the end of treatment; but only 41% maintained their status over a 5 year period.

Reports of results with electric shock treatment of schizophrenics have varied from 10% improvement (Smith *et al.*[47]) to 70% improvement (Kalinowsky[28]). Kalinowsky emphasized the importance of continued treatment in spite of early clinical improvement, frequently employing 20 or more shocks in contrast to the 10 or so used by others. "Discontinuance of treatment after the usually early clinical improvement leads almost invariably to relapse and is the most important reason for failure of the method in the treatment of schizophrenia."

Other procedures which have recently been suggested in the treatment of schizophrenia include bilateral prefrontal lobotomy ("psychosurgery"[13]), "electronarcosis"[51] and "pyretoelectric shock therapy."[15]

Prognosis. All agree that acute onset and short duration of the psychosis are favorable prognostic signs. Terry and Rennie[50] have summed up the factors contributing to a good prognosis in schizophrenic patients as: "Sympathetic environment to which they can return; interests, goals, and pursuits in keeping with their ability; onset of the psychosis in a setting of unusual strain possible to modify; intact rapport and the combined will and ability to coöperate. Special features of the psychosis that seem prognostically valuable are evidences of intact thinking and personal appearance, absence of hallucinatory phenomena, affective admixtures in the psychoses, or the presence of a temporary infectious process at the onset or during the psychosis."

Lewis[36] has studied prognosis from the standpoint of prepsychotic factors (heredity, morphologic type, character, social factors, intellect and trauma), the initial stage of the psychosis (age at onset, insidious or sudden onset and exogenous precipitating factors), the symptoms of the acute stage, and the course of the disorder (steadily progressive, tendency to remission, catastrophic development). Some favorable prognostic factors are said to be: pyknic habitus, cycloid temperament, vigorous emotional response (especially depression) at the onset, active exogenous precipitating factors, and amnesia for the acute phase.

Summary and Conclusions. The term schizophrenia should be used to designate, not an isolated disease entity, but a psychiatric reaction seen in certain ("susceptible") individuals as the result of a more or less prolonged difficulty in adjustment—a "disorder of living." An all-inclusive definition of the term is difficult because of the myriad patterns of expression in different individuals and, often enough, in the same individual at different times. Common findings in the schizophrenic reaction include vague, autistic thinking, lack of interest and progressive withdrawal from the realities of life, peculiarities of emotional expression or an *apparent* emotional indifference, delusions and hallucinations, *apparently* incoherent or irrelevant language, and bizarre motor behavior such as catatonia.

The attempt to pigeonhole schizophrenic patients into a number of specific categories has been relatively unproductive. No present classification contains mutually exclusive subdivisions. We are not even certain of any clean-cut demarcation between the psychoneurotic reaction and schizophrenia on the one hand and between the manic-depressive reaction and schizophrenia on the other. More understanding is to be gained by studying the

patient and his life as an individual problem rather than by studying him as a representative of a nebulous subdivision.

The suggestion has been made that 2 different types of disorder are included in the total group. One is said to be an insidious, chronic malady with a uniformly poor prognosis and is presumed to be due to deteriorative disease of the central nervous system. The other type is said to have a more acute onset, a relatively good prognosis and to be of psychogenic origin. There is little question that the prognosis is poorer when the onset is insidious and when the disorder has been present for a long period of time; this applies to either treated or untreated patients. Hence, such a thesis may be of some practical importance in the treatment of schizophrenic patients. There is, however, no adequate proof that 2 etiologically different groups exist or that the difference between the 2 is a qualitative rather than a quantitative one.

The search for a single etiologic factor has been uniformly disappointing to about all but the individual proponent of his own theory. The inheritance of schizophrenia has been said to follow one or the other type of Mendelian transmission. Suggestions have been offered that the inheritance is of the simple recessive type, the dominant type, or of a mixed type in which a number of primary and secondary genes play a rôle. While there is little doubt that psychiatric disturbances are more frequent in the family of schizophrenic patients than in "normals," the number of divergent views of those favoring an hereditary origin is in itself evidence that present statistical evidence is inconclusive. We are unable to state with any degree of certainty the relative rôles of inheritance (or "constitution") and the effect of psychiatrically handicapped relatives as environmental liabilities contributing to maladaptation. It is probable, however, that the relative rôle of each varies with each patient.

The results of both neuropathologic and metabolic studies are so conflicting that the unbiased observer is all but overwhelmed by confusion. The few variations that have been noted with any degree of consistency may prove to be as readily explainable as the effect rather than as the cause of the disorder. It is well to bear in mind, however, that a number of organic diseases involving the cerebrum may precipitate a schizophrenic syndrome, and differential diagnosis may be difficult. This is especially true of catatonic syndromes.

Studies of the life history of schizophrenic patients have without doubt thrown more light upon the understanding and treatment of the schizophrenic reaction than all of the multitudinous hereditary, pathologic and metabolic researches. Such studies are time-consuming and difficult to express statistically. Yet but few who take the time to carry them out can help but be convinced of the importance of life factors in contributing to the insecurity and maladjustment of the individual and the development of the schizophrenic reaction.

Such factors, however, have not offered the entire solution to the problem of etiology. We have inadequate psychologic explanations to explain the development of psychoneurotic reactions in certain individuals and of schizophrenic reactions in others as the result of apparently similar psychogenic stresses; indeed, we have no proof that these same psychogenic stresses may cause no particular psychiatric disturbance in still others. The postulate that the psychologically traumatic experiences of schizophrenics appear earlier in life than those of psychoneurotics can neither be affirmed nor denied with certainty. We are, at least for the present, forced to lean upon the somewhat vague concept of "constitution," by which is generally meant the inborn, hereditary attributes that influence personality structure. Present-day studies correlating morphology and personality may help to clarify this concept.

A great deal of effort has been expended in studying the language, thought and

behavior of schizophrenic patients. It is clear that the language of even the most disorganized schizophrenic is not meaningless. An intimate knowledge of the person and his life may be necessary, however, before the meaning becomes apparent to the observer. Numerous attempts have been made to relate schizophrenic thinking to that of children or of primitive peoples. Hence, in some quarters, schizophrenia is considered a "regressive" disorder. Recently this viewpoint has been rekindled by evidence that schizophrenic language is similar to that of the child or of primitive man in that it is "concrete." There is said to be a defect in "conceptual" (or abstract or categorical) thinking. While this defect is unquestionably present in many instances, considerable doubt remains as to whether it is a basic factor. The fact that a proponent of this viewpoint finds definite impairment in conceptual thinking in less than one-half of a group of schizophrenic patients indicates that it can hardly form the basis for an all-inclusive hypothesis. There is no convincing evidence that patients with impairment of conceptual thinking have a fundamentally different disorder than those in whom it is intact.

Psychometric tests indicate that intellectual disturbances in schizophrenia are not similar to those with organic brain disease. Any apparent reduction in intelligence may be adequately explained in most instances on the basis of emotional maladjustments. Long term psychologic studies of schizophrenic patients show that this apparent intellectual impairment is capable of recovery even after long periods of time. The terms "deterioration" or "dementia," which have been extensively employed, seem to have no useful place in the concept of schizophrenia and had best be reserved for patients suffering from organic brain disease with intellectual dilapidation.

Both shock therapies (insulin coma and electrically induced convulsions) and psychotherapeutic methods have their place in the treatment program. There is, unfortunately, the tendency to employ shock therapy without reference to the personality problems of the patient. The use of isolated shock therapy has undoubtedly contributed to the large number of relapses. On the other hand, reliance solely upon present methods of psychotherapy may necessitate a prolonged and expensive hospitalization which can only apply to the select few. Unfortunately, at the present time no adequate studies of shock therapy combined or followed with intensive psychotherapy have appeared. If the concept of schizophrenia as a "disorder of living" is correct, the isolated use of any shock procedure without reference to the personal and interpersonal problems of the individual patient cannot be expected to lead to long-term improvement.

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PHYSIOLOGY

PROCEEDINGS OF

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Effect of Concussion Upon the Polarizability of the Brain. E. A. SPIEGEL, M.D., G. C. HENNY, M.D., H. T. WYCIS, M.D., and M. SPIEGEL-ADOLF, M.D. (Depts. of Experimental Neurology, Colloid Chemistry and Physics, Temple Univ. School of Medicine, Philadelphia, Pa.). The polarizability of the cerebrum was studied in cats and guinea pigs following concussive and subconcussive blows produced by a pendulum. After subconcussive blows, no significant change of polarizability was found, while a significant decrease occurred following severe concussive blows. This change indicates an injury to cell membranes in the cerebrum; it is a reversible process, and it appears also in animals kept under artificial respiration. The impairment of the polarizability of the cell membranes, together with some changes affecting the interior of the cells, belongs to a group of secondary changes reaching a maximum after the fleeting functional disturbances characteristic for concussion have subsided. (Appeared in *Am. J. Physiol.*, **146**, 12, 1946.)

Direct Measurement of Coronary Blood Flow in the Anesthetized Dog. J. E. ECKENHOFF, M.D., and C. M. LANDMESSER, M.D. (Dept. of Pharmacology and Harrison Dept. of Surg. Research, Univ. of Penna.). In heparinized dogs anesthetized with nembutal or morphine-chloralose, blood was circuited from a carotid artery through a bubble flowmeter into a cannulated left descending or circumflex coronary artery. The chest was then closed and spontaneous respiration resumed. Flow readings before and after closure of the chest showed significant differences. Under the conditions of these experiments the mean "normal" coronary blood flow was 64 cc. per 100 gm. of heart tissue (coefficient of variation ±11.2). A striking parallelism of blood pressure and coronary blood flow was observed, a given percentile drop in blood pressure usually resulting in an approximately equal percentile drop in flow. Electrical stimulation of cardiac sympathetic and parasympathetic nerves gave no evidence of vasoconstrictor innervation to the coronary vessels. Epinephrin injected into the coronary artery produced immediate and brief increases of flow independent of change in blood pressure and pulse rate. Acetylcholine intra-arterially had similar effects tending to be more marked and more transient. When the common vasodilators were given systemically, papaverine intravenously produced the most significant and sustained increase in coronary flow with a minimum of side reactions. Aminophylline intravenously acts much the same but caused a prolonged increase in pulse rate. Amyl nitrite inhalation produced marked increases in flow (even with decreases in blood pressure) and violent increases in pulse rate. Nitroglycerin, intravenously, intramuscularly and sublingually was less dramatic and its effects were more dependent upon the maintenance of blood pressure. If the pressure fell, the coronary flow decreased. Nikethamide was found to be without significant coronary vasodilator effect when administered intravenously in dosage ranging from 125 to 750 mg. Preliminary observations upon cardiac metabolism indicate the average arteriovenous (coronary sinus) oxygen difference to be 12 to 15 vol. %. The simultaneous systemic (right auricular or ventricular) arteriovenous difference was

about 7 vol. %. There is no significant alteration of the coronary A–V difference under nembutal, cyclopropane, or morphine anesthesia. The oxygen uptake for the normal "resting" heart appears to be about 6 cc. per 100 gm. of heart per minute.

Cerebral Blood Flow and Cerebral Oxygen Consumption in 5 Patients With Hypertension. SEYMOUR S. KETY, M.D., and CARL F. SCHMIDT, M.D. (Dept. of Pharmacology, Univ. of Penna., and Medical Services, Phila. Gen. Hosp.). A knowledge of cerebral hemodynamics should be of considerable importance in the study of arterial hypertension for a number of reasons. Cerebrovascular complications are of great frequency in the disease and many of the symptoms are directly referable to the brain. Recent studies of renal physiology in hypertension have served to diminish the importance of the kidney as a primary etiologic factor in this disease. At the same time the experiments of Fishback and associates, and of Novak and Walker, who produced intense and persistent hypertension by artificial restriction of cerebral blood flow have reawakened interest in the rôle of central mechanisms in this disease. There have to date been no definitive studies on cerebral blood flow and metabolism in clinical hypertension; the only attempts which have been made in this direction by Raab (*Ztschr. f. klin. Med.*, **115**, 577, 1931) and Williams and Lennox (*Quart. J. Med.*, **8**, 185, 1939) used cerebral arteriovenous oxygen differences as measures of cerebral blood flow, a presumption which is unwarranted without concomitant knowledge of cerebral oxygen consumption. In the present study quantitative measurements of cerebral blood flow were obtained in 5 patients by the use of the nitrous oxide method previously described by the authors (*Am. J. Physiol.*, **143**, 53, 1945). Mean arterial blood pressure was determined by a damped mercury manometer attached to a needle in the femoral artery. Cerebral oxygen consumption was calculated from the values for cerebral blood flow and the cerebral arteriovenous oxygen difference and cerebral vascular resistance from the cerebral blood flow and the mean arterial blood pressure. In the 5 patients thus far studied the following mean values were found: auscultatory blood pressure 190/122 mm. Hg, mean arterial blood pressure 143 mm. Hg, cerebral blood flow 64 cc. per 100 gm. of brain per minute, cerebral O_2 consumption 3.6 cc. per 100 gm. per minute and cerebral vascular resistance 2.3 mm. Hg per cc. blood flow per 100 gm. per minute. These values may be compared with the means of 35 experiments on 15 normal young white males where values were found of: 110/80 mm. Hg, 92 mm. Hg, 70 cc. per 100 gm. per minute, 4.3 cc. per 100 gm. per minute, and 1.2 mm. Hg per cc. per 100 gm. per minute respectively. With the limitation in mind that the hypertension patients were somewhat older than the control group and included 4 Negroes, it is seen that there is a slight reduction in the average cerebral blood flow and cerebral oxygen consumption and a marked increase in the cerebral vascular resistance of the hypertensives as compared to normal. Whether any of these changes are statistically significant must await the results of a larger series of hypertensives and a more comparable group of normals. In the small series reported it is interesting to note that the cerebral blood flow decreased and cerebral vascular resistance increased with increasing severity of retinoscopic changes, lending credence to the clinical impression that retinal vascular changes reflect those occurring in the brain. The progressive but only moderate decrease in cerebral blood flow as the disease progresses in this small series is exactly analogous to the findings of Goldring *et al.* (*J. Clin. Invest.*, **20**, 637, 1941) in renal blood flow. The marked increase in cerebral vascular resistance which we have found and its similarity to the changes in renal vascular resistance contributes additional evidence to the con-

cept that the generalized increase in vascular resistance occurring in hypertension is not the result of sympathetic vasoconstriction since extensive work on animals indicates a relatively weak sympathetic constrictor innervation to cerebral vessels (*Physiol. Rev.*, **16**, 545, 1936).

Phase-Boundary Potentials and the Nerve Impulse.* T. CUNLIFFE BARNES, D.Sc., and R. BEUTNER, M.D. (Depts. of Physiology and Pharmacology, Hahnemann Med. Coll. and Hosp. of Phila.). 0.05% acetylcholine produces typical spike potentials on a cholesterol-resin-guaiacol layer (less than 0.01 mm. thick) in saline recorded by an electroencephalograph through Ag–AgCl electrodes in saline on each side of the membrane. The following measurements on thick (2 cm.) oil layers show that acetylcholine is the only substance in cholinergic nerve capable of producing the action current. 0.05% acetylcholine on cholesterol guaiacol gives 35 mv. negative (for great dilutions the sensitive benzoate-nitrobenzene interface must be used). 1% KCl on nitrobenzene gives only 10 mv. negative, 4% sodium lactate on cholesterol guaiacol gives 9 mv. positive, 0.1% dibasic sodium phosphate on guaiacol gives 10 mv. positive, 0.05% choline on cholesterol gives 15 mv. negative. 0.1% sodium acetate gives only 3 mv. positive on guaiacol. Small after-potentials in nerve may result from these products.

0.02% prostigmine (the most electrically active drug tested) generates 48 mv. negative on cholesterol guaiacol: 0.05% eserin gives 27 mv. negative. Measurements by I. Mauer show that 0.05% dilantin and also phenobarbital sodium give 20 mv. positive which reduces the acetylcholine negativity two-thirds explaining their action in grand mal. Tridione, bromide, bromural and metrazol give no phase boundary potentials.

After the passage of an imposed current of 6 volts (less than 1 ma.) the acetylcholine potential on oil is reduced one-third. Electroshock therapy probably alters acetylcholine brain potentials (our EEG's taken on patients after electroshock show slow waves).

One in 10,000 acetylcholine produces 25 mv. negative on frog sciatic and brain and lobster nerve in isotonic glucose (to eliminate short-circuits by salts).

Nachmansohn (*J. Neurophysiol.*, **9**, 9, 1946) poisoned squid nerve with eserine, strychnine, procaine and cocaine and found no evidence for the esterase theory. If esterase is essential for the action current, eserine should prolong only the descending part of the spike but only a general toxic effect was obtained. The esterase theory also fails to explain adrenergic nerves which are represented in our model by triglyceride oils which give potential with sympathomimetic drugs but not with acetylcholine.

Regression of Mouse Sarcoma 37 Produced by Adrenal Cortex Extracts. LYLE V. BECK, PH.D., and IRENE C. DILLER, PH.D. (Dept. of Physiology, Hahnemann Med. Coll. and Dept. of Cancer Chemotherapy, Lankenau Research Inst.). Intraperitoneal injection of 0.5 cc. of Upjohn Co. beef adrenal gland extract resulted in hemorrhage in mouse sarcoma 37 within a few hours, and definite degenerative changes in the tumor cells, notably pyknosis of the nuclei. Over a period of several days there was a gradual decrease in size of the tumor. Tumors in the Carworth Farms female mice usually showed complete regression, the degenerated remains being sloughed off through the skin. Such females kept for several months failed to show reappearance of a tumor. On the other hand the regressions obtained in Carworth Farms males were usually temporary, and the percentage of complete regression in treated males was not perceptibly greater than that occur-

* This work was carried out under a grant from the American Philosophical Society.

ring spontaneously. Repeated injections of extract into males did not result in increase in percentage of complete regression. This tumor grows more slowly and the percentage of spontaneous regressions is higher in females than in males.

Similar effects of adrenal cortex principles on a rat transplantable leukemia have been reported by Murphy and Sturm (*Science*, **98**, 568, 1943, and **99**, 303, 1944) and on a mouse transplantable lymphosarcoma by Heilman and Kendall (*Endocrinology*, **34**, 416, 1944). It is conceivable that antibody reactions potentiated by adrenal cortex steroids might be concerned in the above antitumor effects, and that similar effects would not occur using primary neoplasms. Another mechanism which may be concerned in the inhibition of these particular malignant growths is the well-known shift toward protein catabolism produced by certain adrenal cortex steroids. The shift toward protein anabolism produced by testosterone might then be concerned in the ineffectiveness of adrenal cortex steroids in male mice.

BOOK REVIEWS AND NOTICES

BACILLARY DYSENTERY, COLITIS AND ENTERITIS. By JOSEPH FELSEN. Pp. 618; 145 illus. Philadelphia: Saunders, 1945. Price, $6.00.

THIS volume presents a comprehensive survey of the acute infectious diarrheas, as well as a discussion of chronic enteric disorders which the author feels are etiologically related to them.

The first section of the book discusses the acute diarrheas, with the emphasis almost solely on Shigella infections. Following an opening on historical background, the epidemiologic, clinical, bacteriologic, pathologic and therapeutic aspects of the disease are presented. Much stress is laid on clinical features of these infections, and the author attempts to classify into 7 types what he regards as atypical forms of the disease. Complications are extensively discussed and analyzed. The data dealing with the case incidence of acute diarrheas are thoroughly presented. Also thoroughly discussed are the data revealing the predominance of Shigella infection when cases of "gastroenteritis," etc., are analyzed etiologically. It might have been appropriate in his discussion of the acute colon infections for the author to examine the rôle of Salmonella organisms more thoroughly, as other observers have noted that these infections are often clinically indistinguishable from those caused by Shigellæ.

In the sections dealing with the chronic forms of colitis and ileitis, the author first describes their clinical and pathologic changes Then he presents some detailed case studies which trace the clinical course of individuals with acute Shigella infection who subsequently developed chronic dysentery. These chronically ill patients the author thinks after thorough study are typical of those usually designated as chronic ulcerative colitis and chronic distal ileitis. Various other concepts concerning the etiology of chronic ulcerative colitis are briefly mentioned. The volume is profusely illustrated with charts and photographs of Roentgen rays and pathologic specimens, especially the section dealing with the chronic diseases.

It is somewhat unfortunate that the text tends to present the author's opinions onesidedly. Especially so, since a number of hypotheses are presented with no documented basis in fact (such as the view that as many as 6 types of toxin are produced by the Shigella organisms; and the view that the chronic ulceration in chronic ulcerative colitis is *due* in most instances to secondary non-specific invaders, "chiefly the enterococcus, hemolytic and non-hemolytic *E. coli*," organisms which are part of the normal bowel flora anyway). However, if the volume is a bit less than scholarly in places, its publication at this time, with its enormous bibliography, by an investigator with such wide clinical experience in these disorders, certainly fills a great need in current medical literature, and should stimulate further study. S. H.

NEW BOOKS

Cornell Conferences on Therapy. By HARRY GOLD, M.D. (Managing Editor), DAVID P. BARR, M.D., EUGENE F. DUBOIS, M.D., MCKEEN CATTELL, M.D., CHARLES H. WHEELER, M.D. Pp. 322, 1st vol. New York: Macmillan, 1946. Price, $3.25.

American Foundations for Social Welfare. By SHELBY M. HARRISON, General Director, Russell Sage Foundation; and F. EMERSON ANDREWS, Director of Publications, Russell Sage Foundation. Pp. 249; director of 505 Foundations. New York: Russell Sage Foundation, 1946. Price, $2.00.

The Principles and Practice of Tropical Medicine. By L. EVERARD NAPIER, Companion of the Order of the Indian Empire; Fellow of the Royal College of Physicians of London; formerly Director and Professor of Tropical Medicine; Consultant to the Secretary of War; Visiting Lecturer on Tropical Medicine, Army Medical School; Visiting Lecturer on Tropical Medicine, Harvard Medical School, Boston; formerly Visiting Professor of Tropical Medicine, Tulane University, New Orleans; formerly Visiting Professor of Medicine, New York University. Pp. 917; 185 illus. New York: Macmillan, 1946. Price, $11.00.

Journal of Gerontology (Non-technical Supplement), Winter No., Part I and Part II. Pp.: Part I, 152; Part II, 184; Vol. I, No. 1, published quarterly for The Gerontological Society, Inc. Springfield, Ill.: Thomas, 1946. Price, $6.00 a year.

"*To Add Life to Years, Not Just Years to Life.* The authorized and official journal of the Gerontological Society, Inc., publishing each quarter, basic materials on problems of aging from the natural and social sciences and the humanities. The non-technical supplement is published in corresponding issues with digests from scientific journal, rewritten for the layman in a non-technical, easy-to-understand manner."

Doctors East, Doctors West. By EDWARD H. HUME, M.D. Pp. 278; 21 illus. New York: Norton, 1946. Price, $3.00.

Renal Diseases. By E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis, Minn. Pp. 434, 115 illus. Philadelphia, Lea & Febiger, 1946. Price, $7.00.

The Biology of Schizophrenia. By R. G. HOSKINS, PH.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School and Worcester State Hospital. Pp. 191. New York: Norton, 1946. Price, $2.75.

German for the Scientist. By PETER F. WIENER, Modern Language Master at Rugby School (formerly Tutor in German in the University of London). Pp. 239. American ed. Brooklyn, N. Y.: Chemical Publ. Co., 1946. Price, $3.50.

A History of Medicine. By DOUGLAS GUTHRIE, M.D., F.R.C.S. (EDIN.), F.R.S.E. Pp. 449; 72 illus. Philadelphia: Lippincott, 1946. Price, $6.00.

A Textbook of Biochemistry. By PHILIP H. MITCHELL, PH.D., Robert P. Brown Professor of Biology, Brown University. Pp. 640; 69 illus. New York: McGraw-Hill, 1946. Price, $5.00.

NEW EDITIONS

Electrocardiography. By LOUIS N. KATZ, A.B., M.A., M.D., F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago, Ill.; Professorial Lecturer in Physiology, University of Chicago, Chicago, Ill. 2nd ed. Pp. 883; 1525 illustrations. Philadelphia: Lea & Febiger, 1946. Price, $12.00.

Exercises in Electrocardiographic Interpretation. By LOUIS N. KATZ, A.B., M.A., M.D., F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago, Ill.; Professorial Lecturer in Physiology, University of Chicago, Chicago, Ill. 2nd ed. Pp. 288; 307 illus. Philadelphia: Lea & Febiger, 1946. Price, $6.00.

Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), University of Southern California; Senior Attending Physician in Neurology and Assistant in Neuropathology, Los Angeles County Hospital, Los Angeles, Calif. 2nd ed. Pp. 292; 60 illus. New York, Hoeber, 1946. Price, $5.00.

Recent Advances in Endocrinology. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. 5th ed. Pp. 415; 76 illus. Philadelphia: Blakiston, 1945.

Autopsy Diagnosis and Technic. By OTTO SAPHIR, Pathologist, Michael Reese Hospital; Professor of Pathology, University of Illinois Medical School, Chicago. Foreword by LUDVIG HEKTOEN, M.D. 2nd ed. Pp. 405; 68 illus. New York: Hoeber, 1946. Price, $5.00.

Psychological Medicine. By DESMOND CURRAN, M.D., F.R.C.P., D.P.M., Psychiatrist and Lecturer in Psychological Medicine, St. George's Hospital, and Honorary Psychiatrist to the Maida Vale Hospital for Nervous Diseases, London; Temp. Surgeon Captain, R.N.V.R., and Consultant in Psychological Medicine to the Royal Navy; and ERIC GUTTMANN, M.D., M.C.R.P., Neuropsychiatric Specialist, Emergency Medical Service; formerly Research Psychiatrist, The Maudsley Hospital, London; Research Neuropsychiatrist, Nuffield Dept. of Surgery, Oxford; Psychiatrist to the Officer Board, National Fire Service. Foreword by J. J. CONYBEARE, M.C., D.M. (OXON.), F.R.C.P., Physician to Guy's Hospital, London. 2nd ed. Pp. 246. Baltimore: Williams & Wilkins, 1945. Price, $3.50.

Synopsis of Obstetrics and Gynecology. By ALECK W. BOURNE, M.A., M.B., B.CH. (CAMB.), F.R.C.S. (ENG.), F.R.C.O.G., Consulting Obstetric Surgeon, Queen Charlotte's Hospital, London; Obstetric Surgeon, St. Mary's Hospital, London; Consulting Surgeon, Samaritan Hospital for Women; Examiner in University of Cambridge; formerly Examiner to Central Midwives Board, and Conjoint Board of England. 9th ed. Pp. 500; 166 illus. Baltimore: Williams & Wilkins, 1945. Price, $5.00.

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